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THE
LARYNGOSCOPE.

VOL. LIX MARCH, 1949. No. 3

HYDROPS OF THE LABYRINTH. CASE REPORT. COAGULATION OPERATION, CLINICAL COURSE AND HISTOPATHOLOGY.

KENNETH M. DAY, M.D.,* Pittsburgh, Pa., and
JOHN R. LINDSAY, M.D.,† Chicago, Ill.

A white male, age 56, was admitted to Pittsburgh Eye and Ear Hospital, March 4, 1942, with a history of repeated paroxysmal attacks of vertigo during the past eight years, associated with a low-pitched roaring tinnitus and gradually increasing deafness in the right ear. The vertigo attacks were described as a feeling of objects rotating from right to left when upright. When lying down, the foot of the bed seemed to drop and objects whirled forward over his head. The duration of the attacks varied from a few minutes to over an hour and were usually accompanied by nausea, vomiting and prostration. The most recent attack occurred a week before admission while the patient was driving a car, causing him to drive off the road and wreck the car. Between the acute attacks of vertigo he frequently felt dizzy and unsteady, and the roaring tinnitus in his right ear was constantly present. He had been under treatment by several doctors during the previous three years. Treatment included ammonium chloride and salt-free diet, also nicotinic acid. He had received no relief from treatment and was desperate. His past medical history was not

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significant except for a tendency to high blood pressure for the past five years.

On local physical examination the nose and throat were negative. The eardrums were in good position and rather opaque. There were no scars visible. Marked diminution of hearing in the right ear. He could not hear a C-4 fork in the right ear. Rinne was positive and the Weber test lateralized to the left ear. No spontaneous nystagmus. Caloric test showed only slightest response from the vertical canals, moderate reaction from the horizontal canals after douching for one minute with water at 52° F. X-rays showed pneumatic mastoids.

General physical and neurologic examinations were negative except for moderate hypertension and arteriosclerosis. B. P., 158/90. Heart slightly enlarged, with some mitral insufficiency.

A diagnosis was made of Ménière's disease or hydrops of the right labyrinth.

Operation March 6, 1942. Through a postauricular incision the mastoid cortex was exposed and the antrum opened by means of drills. The opening into the antrum was enlarged and the outer wall of the aditus removed, thus exposing the incus. The horizontal canal was then skeletonized. A window was made into the horizontal semicircular canal medial to the short process of the incus. The endosteum was removed and the membranous canal could be visualized but did not seem to be distended. A fine needle was passed through the opening in the canal forward into the vestibule. Three applications of a mild coagulating current, of about one-half second each, were then made to the needle. A strong facial spasm occurred with each application. The needle was withdrawn and the mastoid cavity allowed to fill with blood. The incision was closed with clips.

Postoperative convalescence was rapid. The patient was able to sit up and eat the next day. Vertigo was moderate and noticeable only on moving the head. On the fourth day the

patient was able to get out of bed. A spontaneous rotary nystagmus was seen when looking to the left, but was not apparent when the eyes were turned to the right or straight ahead. The roaring tinnitus was still present but was not as loud as before operation. The patient claimed he could hear a radio with his right ear when he stopped his left with his finger. Ten days following operation the patient was walking without assistance. There was some unsteadiness. The wound was healed and the dressing discarded. He was discharged on the eleventh day.

One month following operation he reported that he was free of dizziness. Some difficulty finding his way in the dark. The roaring tinnitus was still present but not nearly so loud as before operation. Hearing in the operated ear was improving, though sounds seemed somewhat "fuzzy" in that ear.

Six months following operation the patient was seen again. He felt fine, was free of dizziness and had gained 20 pounds. He no longer had any difficulty getting around at night. He claimed to be able to hear "twice as well" as before operation. Tinnitus still present, though not constant. A caloric test done at this time produced no response from the right ear when douched with water at 46° F. for one minute. On standing up, the Romberg test was negative. Douching the left ear for 10 seconds produced active responses from all canals.

During the next four years this patient was seen at irregular intervals and he was twice admitted to the hospital for treatment for arteriosclerotic and hypertensive heart disease with congestive failure. On one occasion he reported an objective vertiginous attack lasting 24 hours, accompanied by vomiting, but this was associated with numbness and loss of function of the right side of the body. It was diagnosed as cerebral angiospasm and not labyrinthine disease.

The last otological examination was made in May, 1946. At that time he still had a blowing, soft tinnitus in the right ear and sounds seemed blurred in that ear, though he claimed that he could use the right ear in telephoning. During the next year he developed increasing signs of cardiac decompensation

and finally expired in another hospital of congestive failure in August, 1947. The temporal bones were removed within a half hour and were shipped to Dr. Lindsay for study.

HISTOPATHOLOGICAL EXAMINATION.

The temporal bones were received in 20 per cent formalin solution. They had been removed and placed in the fixative

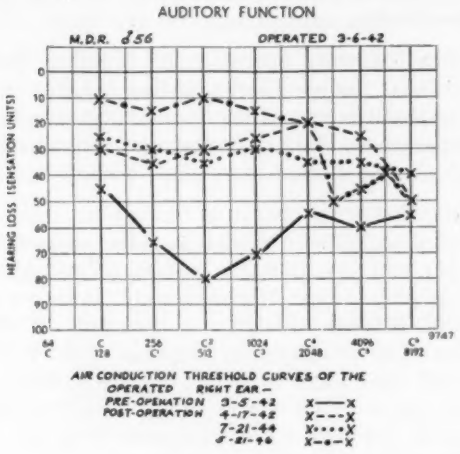

Fig. 1.

solution at about four hours after death. They were decalcified, imbedded in celloidin, sectioned serially, and every tenth section stained with hematoxylin and eosin.

Left Temporal Bone: Middle Ear: The tympanic membrane and middle ear air spaces and ossicular chain were normal. Pneumatization was limited to the mastoid portion.

Inner Ear: The membranous structures were fairly well preserved. The perilymphatic spaces were normal throughout. The endolymphatic system also was normal. Reissner's membrane was in the normal position, and the saccule, utricle

and ampullae of the semicircular canals showed a normal contour throughout. An occasional defect in the membranes had occurred during preparation.

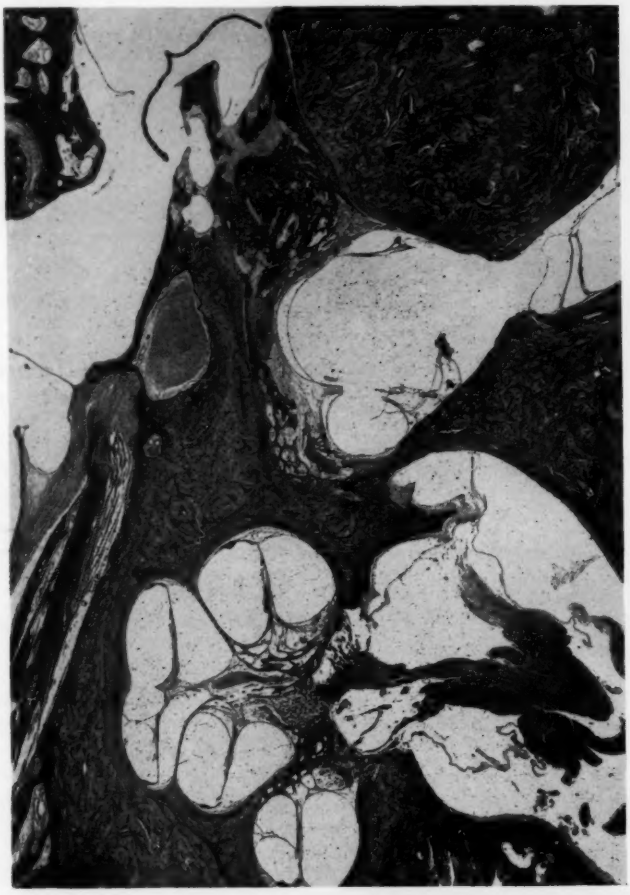

Fig. 2. Horizontal section, right ear. The section shows new bone and fibrous tissue obliterating the horizontal canal ampulla and utricle. The remaining space in the vestibule was occupied by the dilated saccule.

The sense organs in the saccule, utricle and ampullae showed no abnormality.

The stria vascularis appeared approximately normal.

The tectorial membrane was mostly in contact with Corti's organ but was shrunken and thinned out in appearance.

Corti's organ also showed evidence of some shrinkage, the pillars distorted slightly as if by pulling towards the spiral lamina. The hair cells were well enough preserved to determine their presence and showed no evidence of reduction in number (see Fig. 2).

The spiral ganglion showed some reduction in the number of cells in the basal coil.

Comment: The only abnormality found in the middle or inner ear was a moderate decrease in the number of ganglion cells in the basal coil.

Right Temporal Bone: Middle Ear: The eardrum, middle ear proper and ossicular chain showed no significant abnormality. The petrous pyramid was not pneumatized.

The mastoid contained a single large cavity lined by fairly thin mucoperiosteum. There was very little evidence of new bone having formed along the margins. The operative defect had apparently remained its full size and healed without evidence of inflammatory reaction.

Inner Ear: The endolymphatic spaces showed an advanced degree of dilatation (see Fig. 3).

The cochlear duct was dilated to the extent that the vestibular scala was obliterated throughout almost its full extent.

The saccule was extensively dilated, with beginning extension into the small end of the horizontal canal. The saccular macula showed no definite abnormality.

The utricle was almost entirely destroyed and the macula was no longer present. The horizontal canal was filled by new bone and fibrous connective tissue from the ampulla to within

a short distance of the entrance of the small end of the canal into the vestibule. The fibrous tissue, along with some bony trabeculae, extended forward into the vestibule to obliterate the utricular macula and almost all of the space occupied by the utricle. A thin layer of fibrous tissue containing bone

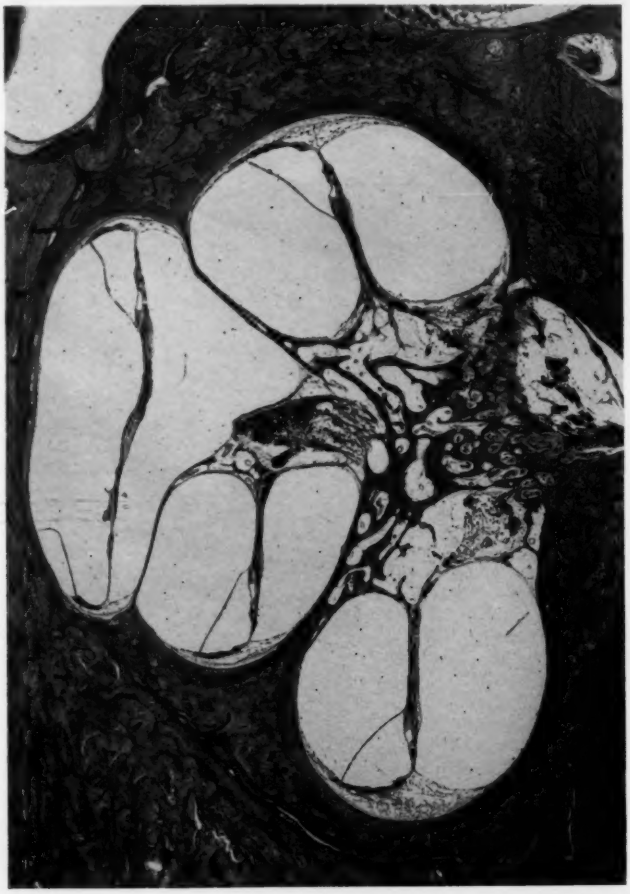

Fig. 3. Left cochlea.

deposits extended down over the inner surface of the stapes footplate. New bone also filled the ampulla of the superior vertical canal and extended upward and around to within a short distance of the common crus. The ampulla of the pos-

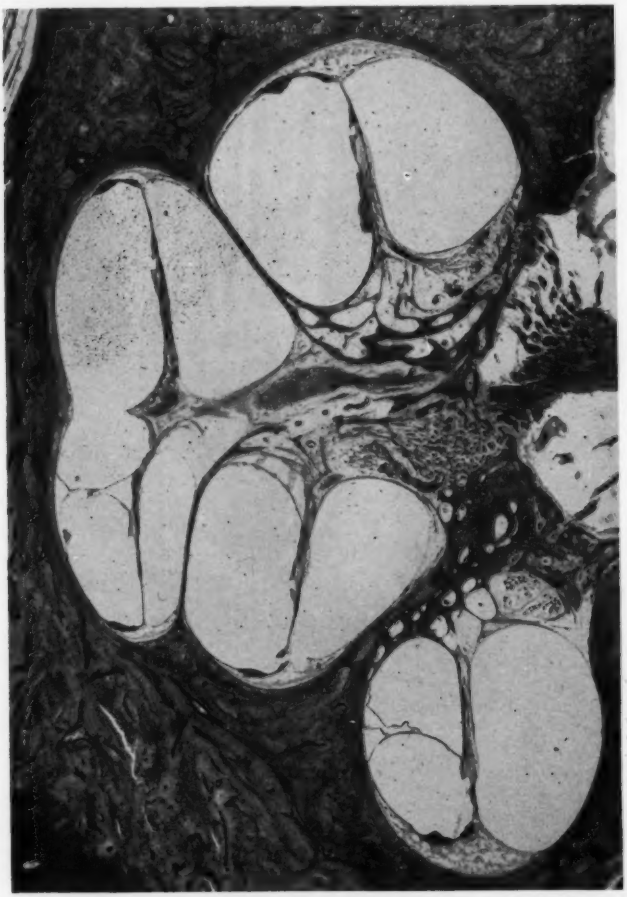

Fig. 4. Right cochlea. Midmodiolar section showing extreme dilatation of the cochlear duct, moderate atrophy of the stria vascularis and degeneration of ganglion cells and nerve fibres in the basal coil.

terior semicircular canal showed distortion of the ampullary wall, but the membranous canal was otherwise normal.

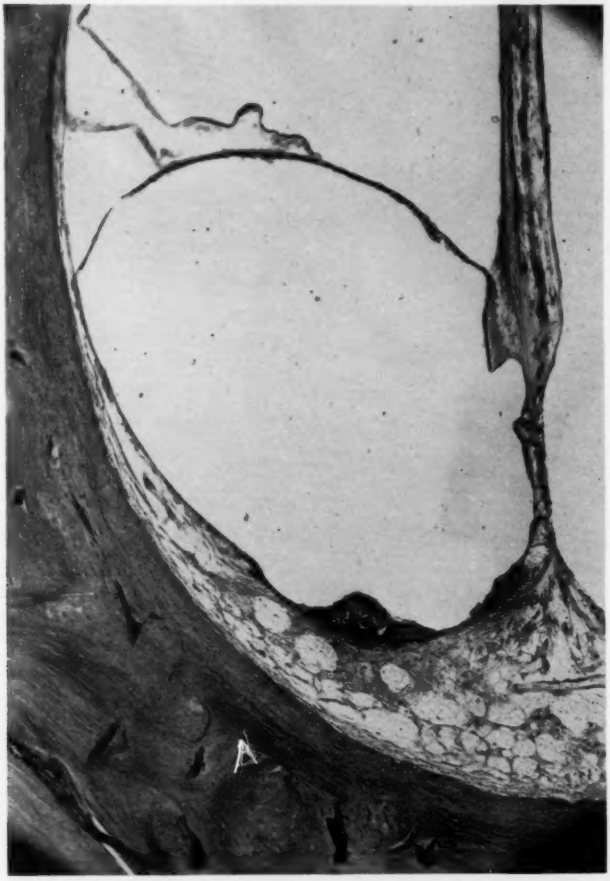

Fig. 5. Right cochlea. Higher magnification of the dilated cochlear duct in the basal coil showing the atrophied stria vascularis and the degenerated Corti's organ. The clear horizontal streak in the central part of Corti's organ represents the tectorial membrane which had apparently become attached and overgrown by cells extending from the lateral margin (cells of Hensen and Claudius).

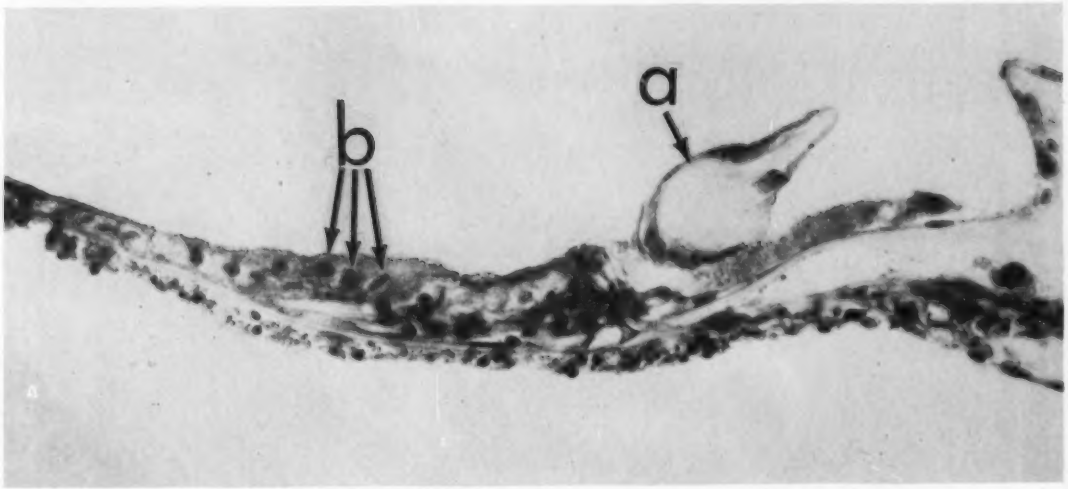

Fig. 6. Corti's organ at the midpoint of the middle coil of the right cochlea. The tectorial membrane (a) was detached at this point. Some of the structures of Corti's organ can be recognized, such as Hensen's cells (b) the base of the inner rod or pillar and the nerve fibres passing up through the basilar membrane.

The nuclei of Deiter's cells are recognizable, but the hair cells have apparently undergone some degree of degeneration. Some distortion has probably occurred, but comparison with the opposite ear indicates that the principal abnormal findings cannot be attributed to artefact.

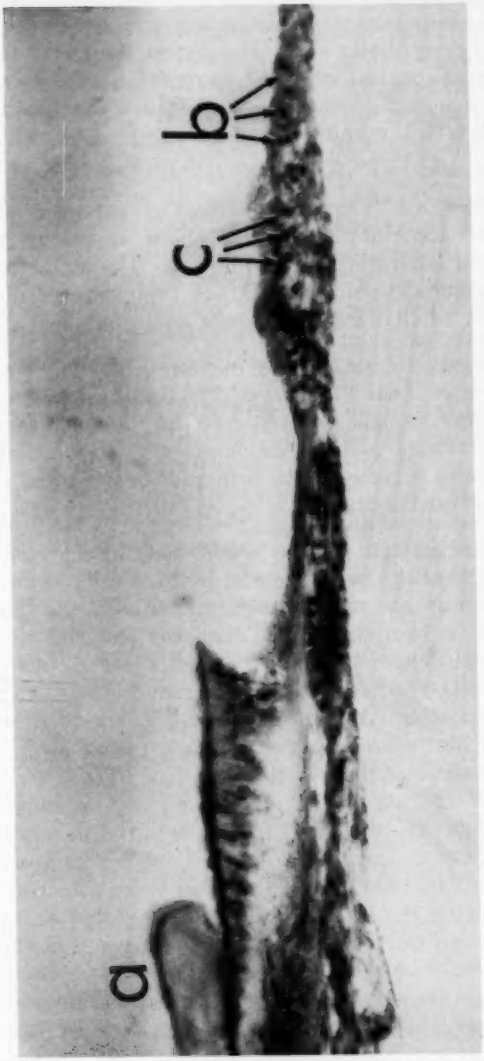

Fig. 7. Right ear. Displaced tectorial membrane (a) Corti's organ appears flattened out, but cells of Hensen (b) and the nuclei of hair cells (c) can be distinguished under the microscope; whether the displacement of the tectorial membrane was present during life cannot be stated.

The endolymphatic duct and sac showed no definite abnormality. The appearance of this structure on the two sides was similar. The vestibular scale was almost completely occupied by the dilated cochlear duct. The tympanic scale was normal except for a mound of loose fibrillar connective tissue attached to the edge of the round window membrane and medial bony margin.

The cochlear duct showed no fibrosis or osteogenesis. There was a small accumulation of amorphous appearing material on the spiral lamina in the middle coil. The stria vascularis had undergone atrophic changes and been reduced almost to half the size of that in the opposite ear.

Corti's organ and the tectorial membrane presented an unusual appearance (see Figs. 5, 6, 7). In the basal coil and extending up through the first half of the middle coil, the tectorial membrane had become detached from the limbus and had apparently become attached to and incorporated into the remnants of Corti's organ.

While the histologic picture is not easily interpreted, it can be observed that the hair cells and Deiter's cells in these coils were apparently absent, but that remnants of the inner and outer pillars were present. The displaced tectorial membrane could be seen draped over these structures and was in turn covered by a layer of cells extending from the cells of Claudius medially almost to its inner free margin, where it could be seen projecting upwards between this covering layer of cells and the remnants of the pillars below (see Figs. 5 and 6). At about the midregion of the middle coil the appearance had changed gradually (see Fig. 6). The tectorial membrane had become less deeply incorporated with Corti's organ and at the upper part of the middle coil was seen to be attached to and partly overlying the limbus while still connected at its tip to the degenerated Corti's organ. In the upper coil the tectorial membrane could be seen lying on the spiral lamina, at some distance from the organ of Corti. The dislocation of the tectrial membrane in the upper coil as seen in the preparations was irregular and may have been due to artefact.

The transition from the conditions found in the basal coil and lower half of the middle coil to that found in the upper end of the middle and in the upper coil had apparently been irregular. At one point near the beginning of the upper coil the tectorial membrane lay up over the limbus and Corti's organ, although, somewhat flattened out, shows a semblance of the normal appearance (see Fig. 7). The pillars were recognizable as well as Hensen's cells, and in the intervening space could be seen nuclei and somewhat distorted cells which undoubtedly were hair cells and Deiter's cells. The flattening out of Corti's organ at this area and in the upper coil is so extreme as to prevent easy recognition of cell structure, but the possibility exists that this flattening out may not have been present during life.

In the upper coil the tectorial membrane was not attached to the organ of Corti but was displaced to some distance. In part of this coil some of the structure of the much flattened out organ of Corti could be made out. The cells of Hensen were most clearly discernible, but the presence or absence of hair cells was usually in doubt. The nerve fibres could be traced to the point where they passed upward through the basilar membrane in all coils.

The spiral ganglion showed a diminution of cells as well as nerve fibres in the basal coil to a greater degree than was seen in the healthy ear (see Figs. 3 and 4).

Summary of Histopathologic Findings: The left ear showed a normal endolymphatic system, a normal cochlear duct, stria vascularis and Corti's organ. Some atrophy of nerve cells in the spiral ganglion of the basal coil was present, but not greater than is commonly found in this age period.

The right ear contained an advanced degree of hydrops of the so-called "idiopathic" type.

The coagulation procedure had destroyed the ampullae and all of the proximal limbs of the horizontal and superior vertical canals and the utricle. New bone and fibrous tissue

replaced these structures, the latter extending down to cover all but the lower margin of the stapes footplate.

The vestibular scala was obliterated by the dilated cochlear duct. The stria vascularis showed moderate atrophy.

Corti's organ and the tectorial membrane were fused together in the basal and most of the middle coil with an apparent obliteration of hair cells. The nerves could be seen passing up through the basilar membrane into the remnants of the organ of Corti.

In the upper coil the structure of the organ of Corti could be more clearly distinguished. In some slides the presence of hair cells as well as their supporting cells seemed fairly definite. There was a slightly greater degree of atrophy of ganglion cells and nerve fibres in the basal coil than in the opposite ear.

The operative cavity in the mastoid had shown no tendency to fill in with new bone, but had become a large air cell lined by thin mucoperiosteum.

COMMENT.

Certain points of significance have been demonstrated by this case.

The mastoid defect showed no tendency to fill in with new bone. Practically no signs of osteogenesis were evident along the margins.

The coagulation procedure had accomplished the objective in destroying the utricle and two semicircular canals. The posterior canal and the saccule were still present, while the saccular macula appeared normal.

The presence of good hearing in this ear seems difficult to understand in view of the condition of Corti's organ and the tectorial membrane in the basal and middle coils. The existence of a Corti's organ which might be capable of function in at least part of the upper coil seemed fairly definite, but the histopathologic appearance of the tectorial membrane, and the

component parts of Corti's organ in the basal and nearly all of the middle coils strongly suggested degenerative changes incompatible with function. The conclusion seems indicated that the extent of auditory function represented in Fig. 1 may have occurred without the aid of sensory cells in the basal and middle coils.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1949 ESSAY CONTEST.

The Ninth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1949. The Society will offer a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Fourteenth Annual Meeting of the Mississippi Valley Medical Society to be held in St. Louis, Mo., Sept. 28, 29, 30, 1949, the Society reserving the exclusive right to first publish the essay in its official publication — the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5,000 words, and must be received not later than May 1, 1949. The winning essays in the 1948 contest appear in the January, 1949, issue of the *Mississippi Valley Medical Journal* (Quincy, Ill.).

Further details may be secured from Dr. Harold Swanberg, Secretary, Mississippi Valley Medical Society, 209-224 W. U. U. Building, Quincy, Ill.

THE NATURE OF BELL'S PALSY.*

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St. Paul, Minn.

When an apparently normal and healthy individual awakens in the morning and finds as he glances in his shaving mirror that he has lost the power of movement of one side of his face, he is said to be suffering from Bell's palsy. This is not, however, the condition originally described by Charles Bell, F.R.S., before the Royal Society in London in 1812.[1] At this time his concern was with the proper allocation of motor and sensory nerve distribution to the facial region, because of the accepted practice of dividing the peripheral trunk of the VIIth cranial nerve for the relief of tic douloureux. Through various case histories and experiments he brought forth conclusive evidence that the "portio dura" of the VIIth nerve had purely motor function and had no place in the genesis of facial pain. His cases included peripheral facial paralysis due to wound from a pistol ball; due to injury from the horn of an ox; and due to operation for extirpation of a tumor before the ear. His careful research, thoughtful clinical observation and compelling presentation established the concept of the motor VIIth and sensory Vth which is today accepted as a matter of course. In the intervening century, peripheral facial paralysis has been shown to result from a variety of causes, including trauma, infection and neoplastic compression. Still, there exists a formidable number of cases not ascribable to any of these agents. It is this residual group which today, for want of an etiologic description, retains the title of Bell's palsy.

Many facts are known about this residual group. The paralysis is rather sudden in onset — usually a matter of hours. Though it has been described as painless, actually pain

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about the ear is a not uncommon symptom in the first 48 hours. Sex has no influence. The adult age group is most commonly afflicted. There is a definite familial incidence. Predisposition as evidenced by recurrences has some importance.[2,3] There is no apparent seasonal incidence.[4] Abnormal cooling of the auricular region has been cited as a cause in as high as 70 per cent of cases.[5] In the absence of this physical exposure, severe emotional upset or shock has been shown to be a precipitating factor.[5]

Repeated thorough general examination has failed to show common systemic organic causation. There are no constant local findings in the peripheral course of the facial nerve, though it is surprising how commonly the vessels of the posterior aspect of the deep portion of the external auditory canal and of the tympanic membrane show notable injection in the first days of involvement. The nerve may be involved in a segment to include the stapedial and the chorda tympani branches or involvement may be below that level. Paralysis may be partial or complete; it may be permanent. Faradic response may disappear in 10 days or two weeks, or recovery may occur without the loss of faradism. Eighty-five per cent of cases regress spontaneously, fully or in large part. There is no established prognostic sign other than the completeness of paralysis or the loss of faradism. There is no unanimity as to etiology or treatment — medical or surgical.

Until recent years the actual changes in the nerve trunk which destroyed its conductive function were largely a matter of conjecture. Few reports of the microscopic changes in the nerve were available and few gross observations of the diseased nerve had been made. Following the basic work of Ballance and Duell,[6] and encouraged by their dictum to operate and decompress the nerve once paralysis is established, many cases of Bell's palsy have come under surgical care and there has been opportunity to observe grossly the disordered trunk in various periods after the onset of paralysis.[3,7,8] There is uniform agreement that the usual finding upon surgical exposure is edema of the nerve with the trunk most tightly constricted by the nerve sheath at its point of issuance from the

stylomastoid foramen. Edema is not a universal finding, however. The nerve trunk may have a normal macroscopic appearance. Kettel[8] has observed further that aseptic necrosis of adjoining portions of the temporal bone presumably due to ischemia is not uncommonly present. This has not been confirmed by others with significant experience.

Compression due to edematous swelling suggests an obvious source of paralysis. Actually, failure of nerve conduction due to change in a localized segment of nerve trunk does not result from compression unless the latter is sufficiently severe to disrupt the axis cylinder. This degree of compression does not occur clinically. Denny-Brown and Brenner[9,10] have shown that conduction failure is a result of ischemia as a primary cause, not compression. Hence, the paralysis of the facial nerve is a result of local vascular change which by ischemia has interrupted conduction and by attendant changes in the local circulation may or may not produce edema. If edema does form, the resulting compression may make the problem of relieving ischemia more difficult.

In a patient in apparent good general health the question may be asked, "Why and by what mechanism is ischemia and edema produced in so localized a region?" It is apparent that it is not dependent on change in the blood elements, or in blood chemistry, or in the permeability of endothelial tissues generally. To be thus localized, it must result from dynamic local vasular change. The probable mechanism has been described and given experimental basis by Abell and Schenck.[11] The essential features are arteriolar constriction; followed by capillary dilatation due to ischemic damage or reflux from venous tonus; a widening of space between endothelial cells;[12] and resultant transudation. To fully understand this sequence the basic work of Krogh[13] on capillaries, and Hudack and McMasters[14,15] on lymph capillaries must be appreciated. The pressure of fluid transudate is rapidly transmitted to the walls of the lymph capillaries and they may be closed by compression. Additional fluid then accumulates and compression of capillaries and venules creates further zonal ischemia and a blanched wheal results. This dynamic mechanism of ischemia

and edema formation has been shown to result from the precipitant influence of physical exposure or emotional stimuli in certain individuals who have an inherent tendency for this eccentric behavior in their arterioles.[16] The impetus to arteriolar constriction in such instance is derived from autonomic nervous impulsion to the involved vessel. It is probable that the tendency is actually inherited through the inheritance of one's autonomic system and its potential imbalances. These imbalances in the head segments are expressed in large part through vagaries in the function of the carotid arterial tree. A high percentage of patients with Bell's palsy give history of other manifestation of carotid vasomotor disturbance: chronic vasomotor rhinitis; vasodilating pain; cervical myalgia; or vasomotor labyrinthitis.

The vessels of most vital physiologic import in any arterial trunk system are the arterioles. Because of the anatomy of their autonomic innervation in the peripheral vascular areas, arterioles tend to behave in segmental arterial branch fashion rather than in diffuse, haphazard manner. When the arterioles of a small segmental branch of the carotid tree constrict simultaneously the resultant ischemia produces interesting clinical conditions in the tissues supplied by that branch. The conditions may vary widely according to the cranial tissue involved. In the case of end-arteries without collaterals, a peripheral cataclysm may occur as, for example, in the inner ear.[17] In a confined anatomic situation where associated edema is able by compression to prevent collateral arterial supply, an analagous condition is created. Edema within the firm fibrous sheath of the facial nerve in the region of the stylomastoid foramen is an example.

There is a collateral arterial supply which can modify the ischemia of the facial nerve produced by widespread arteriolar constriction of the stylomastoid arterial bed. There are two principal anastomoses. The first is that of the terminal branch of the stylomastoid artery with the superior petrosal branch of the middle meningeal through the hiatus for the great superficial petrosal nerve. The second is that of the posterior tympanic branch of the stylomastoid artery which

leaves the facial canal with the chorda tympani and in the posterior aspect of the tympanum and tympanic membrane anastomoses with other branch arteries to the tympanum from the internal maxillary, the ascending pharyngeal, the middle meningeal and the carotid arteries.

Hyperacusis resulting from stapedial nerve paralysis and the loss of taste sensation due to chorda tympani involvement are common in the early period of Bell's palsy. Restoration of the normal function of these two branches commonly occurs in spite of continued facial paralysis. It probably results from early relief of ischemia at the knee of the facial nerve due to these two anastomoses. There is little or no collateral supply to relieve the ischemia below this level.

Spasm in arteriolar terminals can produce dilatation in their arterial trunk. This dilatation in the fine arterial segments of the posterior tympanic branch of the stylomastoid artery accounts for the injection in the region of the posterior annulus frequently seen in the first days of ischemia and palsy. Segmental peripheral spasm may be sufficiently widespread to cause retrograde arterial dilatation in larger branches and in the stylomastoid artery itself. The vasodilating pain produced is that not uncommonly seen with the onset of Bell's palsy. It usually denotes ultimate severe ischemic involvement.

Since this paralysis is an ischemic neuritis, its relief may be expected to hinge upon the restoration of circulation in the involved stylomastoid arterial segments. Immediate nonsurgical measures must be directed toward relief of arteriolar spasm. These may embrace vasodilating drugs with peripheral effect such as nicotinic acid, intravenous histamine or papaverine, or with sympathetic paralyzing effect as ergotamine tartrate or tetraethylammonium chloride; or cervical sympathetic block. The ischemia of the vertical segment of the nerve trunk must be countered through the constricted arteriolar bed, since collateral supply is not present. The secondary factor of compression by edema may be eased by surgical exposure of the involved trunk; however, 85 per cent of cases get eventual satisfactory return of function without this

major surgical procedure. There is no clear-cut early method of determining which individual cases will constitute the unhappy 15 per cent with residual paralysis. An immediate major surgical procedure on all cases to salvage this 15 per cent may not receive wide acceptance.

Motor conduction through the ischemic nerve trunk is interrupted when ischemia results in destruction of myelin sheath.[9,10] This appears first at the nodes of Ranvier. The reaction of degeneration, on the other hand, will not be present until ischemic necrosis of the axon occurs. This clinically occurs most frequently after 10 to 14 days. By this time the most advanced degree of ischemic functional damage is present and a prolonged course is assured. Recovery from this phase commonly results in associated facial movements because it is possible for regenerating axons to cross the necrotic area and progress into wrong myelin tubules. This will be true whether the nerve is now surgically decompressed or not. A significant number of patients with this advanced degree of ischemic damage still make satisfactory spontaneous recoveries. The percentage of such patients has not been accurately determined, but it is high enough to discourage a dictum of universal nerve decompression at the first appearance of the reaction of degeneration, since necrosis is already an established fact.

As long as the opportunity for spontaneous recovery is not being jeopardized by waiting, surgery seems contraindicated. Waiting until fibrosis in the nerve trunk replaces necrosis is certainly unwise.[8,18,19] The time of this transition has not been determined and must depend on variable factors of circulation in the impaired area. It seems probable certainly that this period may be much longer than is commonly accepted, as long as facial musculature is maintained in a receptive state through electric stimulation, support and massage. This view is supported by the infrequent occurrence of fibrosis in surgically exposed nerve with paresis of fewer than six months' duration.

What, then, can surgical decompression offer? First, in the

very nature of surgical trauma to the local area of arteriolar constriction, dilatation may be reflexly stimulated. Second, release of the constricting sheath relaxes pressure on lymph and blood capillaries and arterioles and venules, and mechanically facilitates subsequent vasodilating therapy. Third, circulation to the nerve through normal or collateral channels may be supported eventually by revascularization from adjoining soft tissues.

The principal error in therapy today would appear to be a do-nothing attitude toward nonsurgical measures. It has been encouraged over the years by an absence of conviction regarding the pathogenesis of the palsy. The natural tendency toward the restoration of normal vascular tonus results in spontaneous recovery in 85 per cent of cases. It can be facilitated by therapeutic measures directed to the relief of vasospasm. These are just as important postoperatively, and may enhance the surgical result in cases of long duration which eventually come to surgical decompression, as well as in cases subjected to decompression immediately after the onset of paralysis.

SUMMARY.

Bell's palsy is an ischemic neuritis.

It results from segmental arteriolar spasm.

The latter may also produce edema as a secondary phenomenon.

Therapy should be directed toward the relief of vasospasm.

In some cases it may be necessary to facilitate vasodilating therapy by surgical decompression of the edematous nerve trunk.

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COMPARISONS OF THRESHOLDS FOR SPEECH: WORD AND SENTENCE TESTS; RECEIVER vs FIELD, AND MONAURAL vs BINAURAL LISTENING.*

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In a previous paper[1] one of us has pointed out the theoretical and practical usefulness of knowing the relative difficulty of various tests of the threshold for speech and also the absolute values of these thresholds for normal ears; furthermore, it is useful to know the articulation score, as measured by the "PB" (phonetically balanced) word lists,[2] that a listener would be expected to make at his threshold for speech measured by, let us say, Test No. 9.[3] We may also wish to know the differences between monaural and binaural listening and between listening in a free field and listening to the same material under a receiver.

Some of these comparisons have been made before, notably those between monarural and binaural listening and between "free-field" and receiver listening. Our present findings will serve in part to confirm previous results and in part to extend them to hard-of-hearing listeners. Also they represent an experimental calibration of the particular recordings of the tests and the particular sound systems employed at Central Institute for the Deaf. Let us emphasize again that *the particular numerical values for thresholds for speech and for corresponding articulation scores are valid only for these particular recordings* and then only when they are reproduced over a high-fidelity system. The differences between the

*From the Research Laboratory of the Central Institute for the Deaf. This work was conducted under Contract N6onr-272 between the Office of Naval Research and Central Institute for the Deaf. The experimental material formed part of the basis of a thesis submitted by one of the authors (MRB) in partial fulfillment of the requirements for the degree of Master of Science in Education, Washington University.

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thresholds under different conditions of listening are probably valid for other versions and even for other tests, but they are still restricted to sound systems and room acoustics such as we use for our so-called "field tests."

This report compares the results of a series of hearing tests made on two relatively small groups of listeners. One group had "normal" hearing; the members of the other group were hard of hearing to various degrees. The same individuals participated in all of the tests, and many valid intercomparisons are possible. Some of the results have already been incorporated in a previous paper,[1] but the details of method and many additional data are presented below.

TEST ROOM AND APPARATUS.

The test room and electro-acoustic apparatus used in giving the articulation tests have already been fully described.[6] Briefly, they consist of:

1. A test room with an ambient noise level of 38 db measured with a Western Electric RA-330 sound-level meter, weighting network set at "flat."* With the weighting network set at "40 db," the noise level is not over 33 db. The room is not a true "free-field" room; however, it is lined with three inches of rock wool which provides considerable sound absorption. Tests made with the loudspeaker in this room will, therefore, be referred to as "field" tests rather than "free-field" tests.
2. A high-fidelity electro-acoustic system capable of delivering speech without overload-distortion at sound-pressure levels up to 142 db (through a pair of calibrated PDR-10 receivers) and to 100 db in the field (through a Western Electric 753-B loudspeaker). A suitable dividing network was inserted to deliver the test signal through two attenuators to the two receivers. Each attenuator was capable of introducing up to 110 db of attenuation to eliminate one ear for monaural measurements and to equate the ears for binaural measurements.
3. Additional attenuators and a vu meter for measuring and regulating the sound level in steps of 2 db with an accuracy of $\pm$ 1 db.
4. Electrical transcription reproducer for playing the test records.
5. Operator's microphone and a talk-back system for communication between the test room and the control room.

*American Standards Association Specification Z24-3, 1944.

CALIBRATION.

Room.

A 1000-cycle tone was introduced through the Western Electric 753-B loudspeaker in the sound-treated room. A sound-level microphone was hung at the position of the subject's ears two meters in front of the loudspeaker. The sound-level meter indicated a sound-pressure level of 90 db above 0.0002 dyne/cm^2 when the vu meter read 24 vu. The vu meter was bridged across the primary of the speaker transformer (600 ohms).

Receivers.

A calibrating voltage of 0.1 v. r.m.s. at 1000 cycles was measured across the terminals of the PDR-10 receivers. Measurements were made with a Ballantine vacuum-tube voltmeter. This voltage produces 111 db sound-pressure level (re 0.0002 dyne/cm^2) in a 6 cc coupler according to calibration by the Electro-Acoustic Laboratory, Harvard University. The two receivers used were expressly chosen for their practically identical frequency response characteristics.

DESCRIPTION OF SPEECH TESTS.

1. The Threshold for Speech: Psycho-Acoustic Laboratory Test No. 9.

This test consists of 84 spondaic words (two syllables with equal stress, such as "cowboy" and "baseball"). Each list of 42 words is a different scrambling. Lists are recorded in groups of six at levels progressively lower by 4 db steps. The "No. 9 threshold" is the level, calculated by the tabular method described by Hudgins, *et al.*,[3] at which the listener can repeat correctly 50 per cent of the words. Correction was made for the slight differences in difficulty among the recordings employed.[3]

2. The Threshold for Speech: Psycho-Acoustic Laboratory Test No. 12.

This test consists of simple sentences recorded in groups of four at levels progressively lower by 4 db steps.[3] The "No. 12 Threshold" is the sound level, calculated by the tabular method, at which the listener can repeat correctly 50 per cent of the sentences. Correction was made for the slight differences in difficulty among the recordings employed.[3]

3. The Threshold for Speech: Psycho-Acoustic Laboratory "PB" Word Lists.

Recordings of eight of the 50-word, phonetically balanced lists of monosyllables developed at Psycho-Acoustic Laboratory[2] were used in this study. The lists are proportionately representative of the phonetic elements of normal spoken English. The lists were recorded in the Technisonic Laboratory at Central Institute for the Deaf with a trained radio announcer as the talker. The lists are recorded at a constant level and are scored as percentage of total items correctly repeated.

DESCRIPTION OF SUBJECTS.

Group I was made up of ten "normal" listeners. All twenty ears were found to be normal by an examining otologist and by audiometric examination. An audiogram was considered normal if it showed no hearing loss of more than 10 db at

any of the octave frequencies from 256 to 4096 cps inclusive. The ages of the group ranged from 19 to 24 years. All but one of these subjects were completely untrained listeners.

Group II consisted of ten hard-of-hearing subjects; four were cases of predominantly conductive deafness, two of mixed deafness, and four had serious nerve involvement. Division into types was determined from the audiograms and the otological findings. Their ages ranged from 26 to 53 years. Table 1 shows the audiometric data for Group II.

Tests were given through the receivers to Group I in the following order:

1. Test No. 9, right ear
2. Test No. 12, right ear
3. Test No. 12, left ear
4. Test No. 9, left ear
5. Test No. 9, binaurally
6. Test No. 12, binaurally

Different forms of both the No. 9 and No. 12 lists were used for each test. Since the two ears of the normal subjects were very nearly equal in acuity for pure tones they were not further equated. Each ear received the stimulus at the same intensity.

The same order was used in the presentation of the tests in the field. Then two PB lists were given at a level of 10 db above the subject's No. 9 binaural field threshold. For all monaural tests in the field the subject blocked out the ear not being tested by inserting a finger in the external canal to give as complete a seal as possible. This method provided sufficient attentuation as the starting levels were never over 50 db (re 0.0002 dyne/cm^2). To insure that the subject kept his head in the same position relative to the loudspeaker, an adjustable head-rest was used and the subject was asked to keep his head in the head-rest during the test.

Frequent rest periods were given between tests to insure against fatigue.

The procedure for Group II differed from that for Group I

TABLE 1.

AUDIOMETRIC DATA FOR HARD-OF-HEARING LISTENERS.

		Hearing Loss in Decibels								
Frequency		128	256	512	1024	2048	2896	4096	5792	8192	No. 9
Subject	Ear										
	R.	60	60	65	60	65	85	80	65	70	62
R. E.	L.	40	45	55	60	60	70	75	65	70	59
	R.	65	55	65	65	55	45	50	35	50	61
M. S.	L.	65	60	65	60	55	45	45	35	50	60
	R.	60	70	75	70	75	75	100	NT	75	72
C. B.	L.	55	65	70	70	70	80	90	NT	80	71
	R.	45	50	55	55	55	65	90	x	x	57
A. C.	L.	40	45	55	45	40	55	55	60	75	51
	R.	20	30	40	65	65	70	65	70	70	50
W. T.	L.	5	10	35	55	65	60	60	55	60	49
	R.	65	55	60	60	55	50	55	60	60	61
M. W.	L.	65	65	70	90	85	75	85	80	x	88
	R.	35	45	50	50	50	55	60	75	65	51
R. H.	L.	40	40	55	55	60	50	85	65	65	58
	R.	55	60	65	70	60	50	55	45	60	69
I. C.	L.	35	45	55	60	55	60	45	55	60	60
	R.	60	60	70	75	75	75	75	75	x	77
M. C.	L.	65	65	75	80	95	80	85	75	80	79
	R.	5	0	10	15	15	15	20	15	30	18
F. D.*	L.	50	55	55	65	75	75	80	75	80	67

No. 9 = Loss for speech as determined by Test No. 9.
x = Indicates that the tone was not heard at the limit of the audiometer.
NT = No test made. * = Test made with opposite ear masked.

in that more articulation tests were administered, but Group II did no listening "in the field." In general the same sequence of tests was followed. For binaural listening, however, the ears were equated by attenuating the starting level in the better ear by the difference in decibels between the right and left monaural thresholds. The two ears were then functionally equal.

RESULTS AND INTERCOMPARISONS.

1. Receiver Listening vs Field Listening; Normal Hearing, Monaural and Binaural.

The mean thresholds for Group I, Tests No. 9 and No. 12, under four conditions of listening are given in Table 2. It is evident that the thresholds are systematically lower for field listening (in our room) than for receiver listening. The differences are slightly greater for Test No. 12 than for Test No. 9 and for monaural than for binaural listening, but these differences are of questionable significance. The difference of about 3 db (average of all tests) between field and receiver listening is real, although not so large as would be expected from the classical data[7] on minimum audible pressure and minimum audible field thresholds for pure tones. The smaller difference in the present series may be due in part to the fact that our field is not a "free" field. It is also due in part to the unusually low average threshold found for Test No. 9 by receiver listening.

2. Test No. 9 vs Test No. 12.

The mean thresholds for these two tests, determined under the various conditions of listening, are given in Table 3. All of the differences are statistically significant at the one-percent level as determined by the "t" test for small samples.[4] The average difference, for field listening, is 4.27 db. This agrees well with the experience of the Psycho-Acoustic Laboratory and the previous experience at Central Institute for the Deaf as to the relative thresholds of the two tests. For receiver listening the difference is greater, namely, 6.64 db. The greater difference appears consistently for right ear, for

TABLE 2.

COMPARISONS OF RECEIVER AND FIELD LISTENING FOR LISTENERS WITH NORMAL HEARING.

			Thresholds in Decibels Above 0.0002 dyne/cm²					
			RECEIVERS		FIELD			
Test	Ear	N	Mean Threshold	SD	Mean Threshold	SD	Diff.	SE
No. 9	R. E.	10	19.40	2.80	17.40	2.98	2.00	0.82
	L. E.	10	19.70	3.23	17.60	2.91	2.10	1.31
	Mon.	20	19.55	2.72	17.50	2.59	2.05	0.75
	Bi.	10	17.70	2.19	16.70	3.13	1.10	0.91
	All tests	30	18.93	2.91	17.23	3.03	1.70	0.58
No. 12	R. E.	10	27.10	3.91	21.40	2.11	5.70	0.96
	L. E.	10	26.20	4.47	22.40	2.33	3.80	1.33
	Mon.	20	26.65	3.89	21.90	1.93	4.75	0.83
	Bi.	10	23.40	3.53	20.70	2.24	2.70	1.18
	All tests	30	25.57	4.29	21.50	2.33	4.07	0.69
No. 9 and No. 12	R. E.	20	23.25	2.57	19.40	2.19	3.85	0.74
	L. E.	20	22.95	3.53	20.00	2.12	2.95	0.93
	Mon.	40	23.10	2.96	19.70	2.16	3.40	0.59
	Bi.	20	20.55	2.60	18.70	2.30	1.85	0.75
	All tests	60	22.25	2.84	19.37	2.27	2.88	0.47

Mon. = Monaural, all ears.
Bi. = Binaural.
SD = Standard Deviation.
SE = Standard Error of the Mean of the Differences.

TABLE 3.

COMPARISONS BETWEEN TEST No. 9 AND TEST No. 12 FOR LISTENERS WITH NORMAL HEARING.

			Thresholds in Decibels Above 0.0002 dyne/cm²					
			No. 9		No. 12		Difference	
	Ear	N	Mean Threshold	SD	Mean Threshold	SD	Db	SE
Receivers	R. E.	10	19.40	2.80	27.10	3.91	7.70	1.48
	L. E.	10	19.70	3.23	26.20	4.47	6.50	1.39
	Av. Mon.	20	19.55	2.72	26.65	3.89	7.10	1.00
	Bi.	10	17.70	2.19	23.40	3.53	5.70	0.92
	All tests	30	18.93	2.91	25.57	4.29	6.64	0.73
Field	R.E.	10	17.40	2.98	21.40	2.11	4.00	0.91
	L. E.	10	17.60	2.91	22.40	2.33	4.80	1.04
	Av. Mon.	20	17.50	2.59	21.90	1.93	4.40	0.70
	Bi.	10	16.70	3.13	20.70	2.24	4.00	0.97
	All tests	30	17.23	3.03	21.50	2.33	4.27	0.55
Receivers and Field	R. E.	20	18.40	3.06	24.25	4.24	5.85	0.95
	L. E.	20	18.65	3.25	24.30	4.04	5.65	0.87
	Av. Mon.	40	18.53	3.15	24.28	4.13	5.75	0.63
	Bi.	20	17.20	2.75	22.05	3.25	4.85	0.68
	All tests	60	18.08	3.09	23.53	4.00	5.45	0.46

Av. Mon. = Average Monaural or average of right and left ears.
Bi. = Binaural.
SD = Standard Deviation.
SE = Standard Error of the Mean of the Differences.

left ear, and for binaural listening. It is important to notice, however, that the absolute value of the normal monaural threshold (receiver) for Test No. 12 is 26.65 ± 3.89 db and for Test No. 9 it is 19.55 ± 2.72 db. The value for No. 12 agrees with the norm of 26 db previously accepted at Central Institute for the Deaf for this test. The value for No. 9 is 2.91 db below our previously accepted normal of 22.5 db. Here again, as in the difference between field listening and receiver listening, the difference that involves the threshold of No. 9 for Group I gives results that agree less well with other comparable data than do our other findings. We are inclined to attribute the aberrant low threshold of No. 9 in this series to the vagaries of small samples. We now accept 22.0 db as norm for Test No. 9.[1]

The differences between the thresholds of Test No. 9 and of Test No. 12 for Group II (hard of hearing) are given in Table 4. These differences are all statistically significant according to the "t" test, and the over-all average difference of 5.31 db is in fair agreement with the 4 db that we expect according to our current standards. Obviously there are no absolute norms with which to compare our values. The difference between No. 9 and No. 12 is the same for our hard-of-hearing subjects who are classified as having "predominantly conductive" hearing loss as for those whose loss is "predominantly nerve."

TABLE 4.
MEAN DIFFERENCES BETWEEN THRESHOLDS FOR TEST No. 9 AND TEST No. 12.

HARD-OF-HEARING LISTENERS USING RECEIVERS			
	N	Mean Difference	SE
R. E.	10	5.95 db	1.11
L. E.	10	5.20 db	0.67
Average Monaural	20	5.58 db	0.63
Binaural	10	4.77 db	0.65
All Tests	30	5.31 db	0.46

3. Monaural vs Binaural Listening.

The comparisons of the mean binaural thresholds with the

average of the monaural thresholds for Group I under the two listening conditions, receiver and field, are shown in Table 5.

In every case the mean binaural threshold is lower than the average monaural, but not all the differences are significant statistically. The series of field tests show smaller differences which are not significant individually; however, if all field and receiver tests are taken together, the difference of 1.78 db in favor of binaural listening should be found by chance alone less than once in 100 times.

The differences between the binaural threshold and the threshold for the *better* ear are very small and are not significant until combined as a group. Then the binaural threshold for receiver listening averages 1.4 db lower, and the difference is significant at the 2 per cent level. For field listening, however, there is no significant advantage for binaural listening over listening with the better ear.*

The results of our comparisons made with receiver listening are comparable with several other studies, although the others have usually employed pure tones or white noise as the stimu-

TABLE 5.
COMPARISONS OF BINAURAL AND AVERAGE MONAURAL THRESHOLDS OF LISTENERS WITH NORMAL HEARING.

	Thresholds in Decibels Above 0.0002 dyne/cm²					
	Mean Av. Mon. Threshold	Mean Binaural Threshold	Difference	SE	t	P
No. 9, Receiver	19.55	17.70	1.85	.60	3.08	.02
No. 12, Receiver	26.65	23.40	3.25	.77	4.25	.01
All Receiver Tests	23.10	20.55	2.55	.50	5.10	.01
No. 9, Field	17.50	16.70	0.80	.72	1.12	.40
No. 12, Field	21.90	20.70	1.20	.56	2.15	.05
All Field Tests	19.70	18.70	1.00	.45	2.22	.05
All tests, Receiver and Field	21.40	19.62	1.78	.35	5.09	.01

t = Critical ratio.
P = Level of confidence. For example, the figure .02 indicates that there are two chances in one hundred that this is not a true difference.
For other abbreviations see Table 2.

*These data are not tabulated in this paper but may be found in the thesis mentioned in the first footnote.

lus or have relied merely on the threshold of detectability (not intelligibility) of speech.

Shaw, Newman and Hirsh,[5] in their review of past experiments using pure tones, reported that the differences found between binaural and average monaural thresholds vary from 1 to 3 db. In one experiment with speech conducted by these authors using Test No. 9 a difference of 3.9 db. appeared. This compares with the difference of 2.55 db in our experiments using Tests No. 9 and No. 12 (see Table 5). They also report that the binaural thresholds were from 1 to 2 db lower than the best monaural threshold. The present study shows a difference of 1.4 db.

Keys used sentences as the stimulus in his study of monaural versus binaural hearing and found binaural thresholds approximately 3.5 db lower than mean monaural thresholds and 2.4 db lower than better ear thresholds when the ears were not equated in sensitivity. The No. 12 sentence test used in the present study would be comparable to the material used in his experiment and our results from its administration show a mean binaural threshold 3.25 db lower than the mean monaural and 2.0 db lower than the better ear threshold.

Evidently the binaural threshold for speech intelligibility behaves very similarly to the binaural threshold for pure tones and the binaural advantage is approximately 3 db.

Several investigators have tried equating the two ears, that is, making them equal in sensitivity, and then measuring the binaural threshold. In the present study this procedure was followed with Group II, the hard of hearing. The difference between the two ears as measured by the respective thresholds on Test No. 9 varied considerably, as might be expected with subjects whose hearing is defective. One case, F. D., was not used in these comparisons as the difference between her ears was so great that it would have been impossible to get a true binaural reading. With the other nine subjects the stimulus to the better ear was attenuated by the difference in decibels between the No. 9 thresholds of the two ears. The two ears were thus made functionally equal.

Table 6 presents the monaural-binaural data obtained for Test No. 9. The differences shown are those by which the binaural thresholds are lower than the monaural.

The mean advantage of 2.83 db for binaural listening on Test No. 9 has a critical ratio of 5.78 and the chances that this is a real difference are much greater than 1 in 100.

The differences between binaural and monaural thresholds on Test No. 12 are not so easily expressed, as the ears were equated according to the results that appeared between the thresholds of the two ears on Test No. 9. The actual differences in thresholds on No. 12 were not always quite the same as those on No. 9. The differences between the reference monaural scores were, therefore, not exactly the same as those used in equating the two ears, and the binaural score had to be compared not only to the more sensitive but also to the less sensitive ear. As the difference between the two ways of computing the score was only about half a decibel it was decided arbitrarily to use the comparison with the better ear. Table 7 shows the advantage for binaural listening on Test No. 12.

TABLE 6.
BINAURAL ADVANTAGE FOR HARD-OF-HEARING LISTENERS: TEST No. 9.

RECEIVER LISTENING: EARS EQUATED.	
Subject	Binaural Advantage
R. E.	4.0 db
M. S.	2.0
C. S.	1.0
A. C.	2.0
W. T.	1.0
M. S.	4.5
R. H.	2.5
I. C.	5.0
M. C.	3.5
Mean Binaural Advantage	2.83 db
Standard Error of the Mean of the Differences	0.49 db

It is interesting that all but one of the hard-of-hearing subjects stated that it was "easier to listen binaurally than

TABLE 7.
BINAURAL ADVANTAGE FOR HARD-OF-HEARING LISTENERS: TEST No. 12.

RECEIVER LISTENING: EARS EQUATED FOR TEST No. 9.	
Subject	Binaural Advantage
R. E.	5.5 db
M. S.	3.0
C. B.	2.5
A. C.	3.0
W. T.	4.0
M. W.	6.0
R. H.	3.0
I. C.	5.0
M. C.	1.0
Mean Binaural Advantage	3.67 db
Standard Error of the Mean of the Differences	0.53 db

The binaural advantage is reckoned from the best monaural threshold for Test No. 12 (further explanation in text).

TABLE 8.
MEAN BINAURAL ADVANTAGE FOR HARD-OF-HEARING LISTENERS: ALL TESTS.

Test	Mean Binaural Advantage	SE	t	P
No. 9	2.83 db	.49	5.78	.01
No. 12	3.67 db	.53	6.92	.01
All tests	3.25 db	.37	8.78	.01

SE = Standard Error of the Mean of the Differences.
t = Critical ratio.
P = Level of confidence.

with one ear alone." The basis for this psychological impression is not easy to identify.

Table 8 shows the mean binaural advantage for each test and for the two combined. All differences are significant and could have happened by chance alone less than once in a hundred times.

The mean binaural advantage of 3.25 db for both speech tests compares almost exactly with the gain of 3.2 db on Test No. 9 found by Shaw, Newman and Hirsh[5] in a series of similar experiments on normal listeners. It is also of the same order of magnitude as the 4.14 db binaural advantage

for speech found by Keys when he equated the ears of his hard-of-hearing subjects.

4. Relation of "PB Threshold" to Test No. 9.

Earlier results from 152 tests on hard-of-hearing patients[8] showed that the PB threshold is 11.25 db above the threshold for Test No. 9. In order to determine experimentally whether this relationship is the same for normal ears, each of the normal listeners in Group I was given two PB lists in the field at a level 10 db above his previously determined No. 9 binaural field threshold. The intensity of the speech was then sufficient for him to make a score of almost 50 per cent. The mean "PB score" for our normal listeners at a level 10 db above their No. 9 thresholds was actually 46.7 per cent with a standard deviation of 6.6 per cent.

The normal articulation curve for the PB word lists rises at the rate of 3.85 per cent per decibel increase in intensity.[1] It is, therefore, easy to calculate the level of the PB threshold and the probable PB articulation score at the No. 9 threshold. A score of 50 per cent would be expected at a level 0.9 db higher than the 46.7-per-cent-correct level, *i.e.*, 10.9 db above the No. 9 threshold. Also at their No. 9 thresholds our subjects would probably understand 46.7 – 38.5 or 8.2 per cent of the PB words. This figure is practically identical with Thurlow, *et al's*[8] calculated value of 8 per cent for normal listeners. We conclude that for normal listeners as well as for hard-of-hearing listeners the PB threshold is about 11 db above the threshold for Test No. 9.

SUMMARY.

Auditory Tests No. 9 (spondee words) and No. 12 (sentences) of the Psycho-Acoustic Laboratory were administered to ten subjects with normal hearing and to ten who were hard-of-hearing. They were given monaurally and binaurally through headphones and, for the "normals," binaurally from a loudspeaker.

Field listening showed a mean threshold for the two tests lower by 2.88 $\pm$ 0.47 db than receiver listening.

By receiver listening the threshold for Test No. 12 was 6.64 ± 0.73 db. higher than for Test No. 9 for the "normals." This rather large difference is due in part to an unusually low mean threshold for Test No. 9 for our group of "normals." The corresponding difference for the hard of hearing was 5.31 ± 0.46 db. Field measurements for the "normals" showed a difference of only 4.27 ± 0.55 db.

For the binaural tests the two ears of the "normal" listeners were not equated for differences in sensitivity. Nevertheless, for receiver listening, the "normals" showed significant advantages of 2.55 db for binaural listening over the average of all monaural thresholds and of 1.4 db over the mean threshold for the better ear. The hard-of-hearing listeners showed a mean advantage of 3.25 db for binaural listening over monaural when the listener's two ears were equated in sensitivity.

The mean threshold of the "normal" listeners for "PB" monosyllabic word lists was about 11 db higher than their mean threshold for Test No. 9.

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POSTOPERATIVE TONSIL BLEEDING. STUDIES OF THE ETIOLOGY, PREVENTION AND MANAGEMENT.*

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Prior to 1945, postoperative tonsil bleeding assumed proportions which seemed to us to be inconsistent with what we considered well planned and executed surgery. It appeared necessary to ascertain the cause and thereby remedy this condition. Therein lies the reason for the study of this subject and this paper presents the results of our efforts.

While an incidence of 5.27 per cent for delayed hemorrhages, occurring after 24 hours postoperatively, seems high, it was found that, compared with many large and carefully controlled operative series, this is a low figure. Hemorrhages following tonsillectomy seem to vary greatly in different communities and with different operators and possibly in different climates.

Physiology: It is desirable to review briefly the physiology and dynamics of hemostasis.

There exists in the blood plasma antiprothrombin, which inactivates the prothrombin. When platelets and tissue cells disintegrate, thromboplastin is released and neutralizes the antiprothrombin. The prothrombin is then free to combine with calcium ions to form thrombin. Thrombin in turn, unites with fibrinogen, which is also in the blood plasma, to form fibrin, the structural basis of the clot. Prothrombin plus thromboplastin equals thrombin. Thrombin plus fibrinogen equals fibrin.

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CHART 1. THE COAGULATION (CLOTTING) OF BLOOD.

The Essential Agents:

1. Prothrombin (a globin)
2. Thromboplastin (lipoids—phosphatides?
3. Calcium
4. Fibrinogen (a globin)

Reacts to form thrombin

1, 2 and 3 interact to form an active enzyme (thrombin) which reacts with fibrinogen, changing it to an insoluble gel (fibrin), which constitutes the clot.

1. Prothrombin plus thromboplastin plus calcium equals thrombin.
2. Thrombin plus fibrinogen equals fibrin* (the clot).

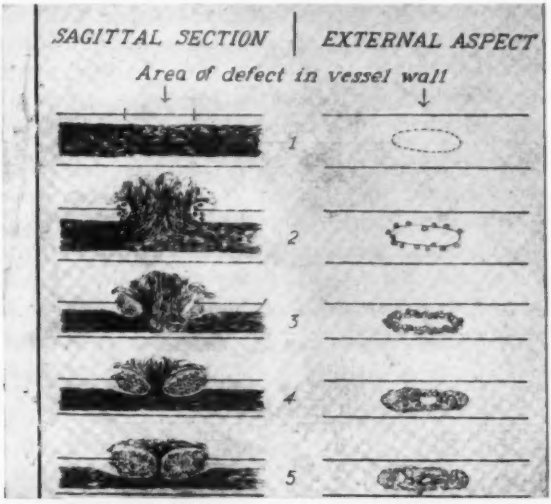

Diagram 2. (1) Intact vessel full of blood. (2) Break in wall of vessel with outflow of blood — leucocytes rush to injured margins. (3) Lumen of vessel constricted by fibrin and leucocyte mass. Flow of blood slowed (4 and 5) Lumen further diminished by increasing hemostatic plug until vessel wound closed off and blood loss controlled.

Dynamics of Hemostasis: Tocantins[2] has graphically shown that immediately after a vessel is severed and blood begins to escape, pressure within it begins to fall and its lumen tends to become smaller. If blood extravasates into the sur-

*Insoluble protein not found in normal blood.

Howell, W. H.: Physiology, 1935.
Quick, A. J.: Jour. A. M. A., 110:1658, 1948.

rounding tissues, the pressure about the vessel builds up and causes the mass of blood to flow through adjacent vessels. The blood flow through the injured vessel is reduced, and the blood is permitted to come into contact with the tissue fluids and platelets to mass at the site of the injury. This may be all that is necessary to control the bleeding from a small vessel by plugging it with a clot.

It is evident, then, that the structure of the vessel wall and the pressure of the blood within largely determine the efficiency of each hemostatic factor. In arteries, when the blood pressure is 100 to 120 mm. of hemoglobin, and in arterioles where it is 60 to 70 mm., massing of platelets and plugging by clot is less efficient than in capillaries and venules where the pressure is 30 to 40 mm. and 10 to 20 mm., respectively.

From this brief survey, it follows that all efforts at hemostasis after tonsillectomy, by means of packs, sponges, contraction, and retraction of the vessel walls by ligatures, clamps, astringents, etc., and the forming of hemostatic fibrin plugs by supplying or aiding the body to produce the substances necessary to blood coagulation, are attempts to aid these processes of the natural mechanism of hemostasis.

Etiology of postoperative Tonsil Hemorrhages: There are many and varied causes of post-tonsillectomy bleeding. Some of these will be dealt with in detail, while others will be mentioned only in passing.

Blood dyscrasias such as hemophilia, leucemia, the purpuras and hepatic diseases interfere with the constituents of clot formation and promote hemorrhage.

In cases of hypertension and sclerosis of the vessel walls, a firmer plug and more extravascular pressure is needed to control bleeding.

Recent acute infections of the tonsils result in engorgement of and increased blood flow in the vessels in and about the tonsils. The presence of chronic infections, including Vincent's and syphilis, interfere with clot formation and may dissolve the clot or even erode a vessel wall. Most of us have

seen these cases associated with delayed hemorrhages, following sudden increase in pain and rise in temperature. Infection is probably a very frequent cause of delayed bleeding, and McGovern[3] reports a decrease in his hemorrhages by the use of sulfathiazole chewing gum. He reported 150 cases of tonsillectomy with only two hemorrhages (1.3 per cent); a series too small to be conclusive.

In 1944, Neivert and his co-workers[4] corroborated previous studies showing that salicylates might cause hypoprothrombinemia. He concluded that aspirin was a major cause of post-tonsillectomy hemorrhages.

TABLE 3.

INCIDENCE OF DELAYED HEMORRHAGES ENCOUNTERED AFTER TONSILLAR OPERATIONS IN THE YEARS 1939-1947.

Without Synkayvite medication			With Synkayvite Medication		
Year	No. of T & A	No. of Late Hemorrhages	Year	No. of T & A	No. of Late Hemorrhages
1939	284	13	1944	385	8
			(no change of technique to this point)		
1940	256	11	1945	483	19
1941	226	16	1946	518	6
1942	303	19	1947	451	3
1943	354	16			
Total	1,423	75	Total	1,837	36
Incidence of delayed hemorrhage 5.2%			Incidence of delayed hemorrhage 1.95%		

In 1945, the author[5] presented a study of 1,808 cases of tonsillectomy performed during the period from 1939 to 1944, inclusive. Twenty-five immediate and 83 delayed hemorrhages were reported in this series. An average yearly incidence of 5.3 per cent delayed hemorrhages was reduced to 2.08 per cent when vitamin K (synkavite — Hoffmann-LaRoche) was given for 10 days postoperatively. Since that time, 1,452 cases have been studied, with 28 delayed hemorrhages. This reduces the percentage of bleeding from 5.27 per cent before the use of vitamin K to 1.95 per cent when vitamin K was used postoperatively.

In this work, an attempt was also made to correlate the hemorrhages with the time of year when infections are most prevalent. The difference in the percentage of bleeding cases in winter months was only 1 per cent greater than those occuring during the summer months. This would tend to minimize the importance of infection on tonsillar hemorrhage.

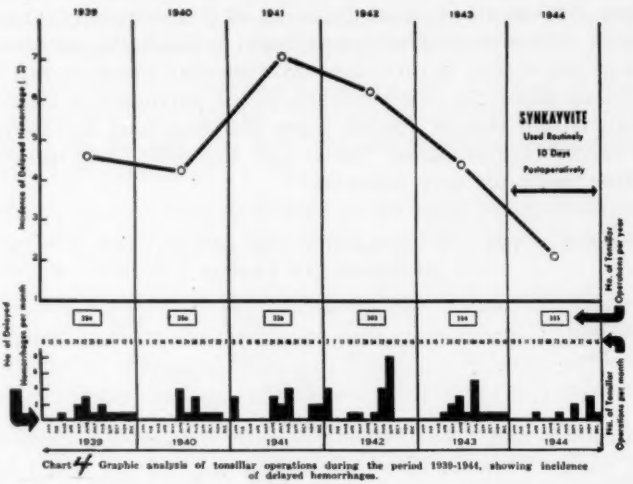

Chart 4. Graphic analysis of tonsillar operations during the period 1939-1944, showing incidence of delayed hemorrhages.

Neivert has pointed out that acetyl salicylic acid in chewing gum may induce postoperative bleeding by some local effect on healing fossa. In this case vitamin K would not be expected to control the tendency to bleed.

More recent studies by Neivert, Pirk and Engleberg[6,7] have demonstrated that in 246 tonsillectomies, those patients with a postoperative subnormal plasma concentration of ascorbic acid had five times as many postoperative hemorrhages as those whose level was normal or above. They presented evidence that vitamin C exerts a protective effect against salicylate induced hypoprothrombinemia, probably due to the vitamin's detoxifying effect.

The author is now studying a series of tonsillectomy cases in which tablets containing ascorbic acid, mg. 100, and synkayvite (Hoffmann-LaRoche, vitamin K), 5 mg., are being used pre- and postoperatively. Too few cases have been observed (125 cases) to justify any conclusions at this time.

Trauma has long been recognized as conducive to secondary hemorrhage in surgical procedures. Torn and injured muscle fibres impede the normal dynamics of hemostasis by interfering with with contraction of vessel walls. If the aponeurosis of the muscle is torn, less extravascular pressure can be built up when the blood spreads to the surrounding tissues. Traumatized tissues, ragged edges and tags lend themselves to excessive granulation tissue and sloughing, and present better media for deep infection.

TABLE 5. TYPE OF OPERATION AND APPLICATION OF TIES In 298 TONSILLAR PATIENTS.

Total T & A Studied	Dissection Operation	Beck-Shenk Snare	No Ties Used	Ties Used	Sutures
298	165	133	235	62	1

Fishman and Lebo[8] (Mayo) recently presented a study of 341 cases of tonsillectomy followed by only 0.5 per cent postoperative hemorrhage. In the absence of medication for the prevention of bleeding, and with the free use of aspirin, they conclude that lack of trauma, attending the use of the Beck snare, was responsible for this low incidence.

During the past year the author has attempted to compare the occurrence of postoperative tonsil hemorrhage in cases in which dissection was employed with those in which the Beck type of instrument was used. In all, 298 cases of tonsillectomy were studied as to the amount of bleeding at the time of operation; and to the relation of postoperative hemorrhage to the type of operation used; and the application of ties.

Of the 298 cases, 165 were dissected and snared. In 133 cases, the Beck type snare was used without dissection. Little

or no difference was noted in the amount of bleeding at the time of operation between the two methods. No postoperative hemorrhages occurred in those cases in which the Beck type instrument was used. While this series is too small to be conclusive, it is, nevertheless, suggestive.

In the 451 cases operated upon in the year 1947, seven hemorrhages occurred. Three of these, or 0.66 per cent, were delayed, and four, or 0.88 per cent, were immediate. The total hemorrhages presented a percentage of 1.5 per cent.

Of the seven hemorrhages occurring, two occurred in cases in which ties were applied. This is suggestive that ties might add to the trauma and may provide excessive granulations which may ooze later.

Other factors, such as suction in the tonsil fossa, or wiping the fossa with gauze, may remove a firm fibrin plug and enhance bleeding.

Symptoms and Signs of Hemorrhage: In adults, the signs of bleeding from the throat are evident, but in small children it might go unnoticed until large amounts of blood are vomited. Pallor, sweating, restlessness, thirst and rapid pulse are systemic evidence of blood loss.

If repeated swallowing occurs, in small children, it should be investigated and it often leads to the detection of early bleeding. Also, we have noted that sudden increase in the amount of pain on one side of the throat often precedes impending bleeding.

Prevention of Hemorrhage: There is no known way to determine which case will have postoperative bleeding; however, a careful history should be taken in an effort to eliminate blood dyscrasias, recent throat infection and family tendencies to bleed. A history of excessive bleeding following injury or tooth extraction, should lead to a careful blood study, including prothrombin time and platelet count. We should expect more bleeding in cases with a history of high blood pressure, arteriosclerosis, recent rheumatic fever, etc.

All of us have seen cases with rapid coagulation time bleed

copiously, and others with a coagulatnon time bleed very little. It seems wise, from every point of view, however, to do a determination of the coagulation or bleeding time just before the operation is to be done. If the coagulation time is found to be more than eight minutes, 10 mg. vitamin K should be given intramuscularly and usually the clotting time will be found to be decreased in an incredibly short time. Also, in cases where preoperative sedation by barbiturates is used, vitamin K should be given.

Ascorbic acid may be given in doses of 100 mg. before meals, pre- and postoperatively. Large amounts of citrus fruit should be taken postoperatively unless they increase the pain, in which case it is better to depend upon the tablets.

Much has been written about the uselessness of giving calcium preoperatively; however, calcium deficiencies do occur rather frequently, especially in goiter belts, and their use routinely may be justified.

Management of Hemorrhage: Primary: Gentle pressure with gauze sponges seems preferable to the many mechanical devices suggested in the past. String sponges are useful in allowing the operator to proceed with the operation on the other tonsil, after removing one. They may be left in the fossa for 10 to 12 hours if desired and usually control oozing. It is seldom necessary to sew the pillars together.

Hemostatic agents such as a solution of thrombin may help to produce a quick. natural clot. A solution should be made of such strength to suit the case and applied directly to the bleeding surface, by means of a sponge. This is especially useful in adenoid bleeding. Oxidized cellulose gauze or cotton may be packed into the postnasal space or tonsil fossa, but should be anchored by a string, so that the material is not aspirated.

The use of astringents or sclerosing substances at the time of the operation should be condemned and gargles do more harm than good.

Crushing the vessel mouth with forceps is preferable to

ligatures or sutures and is usually all that is needed to complete hemostasis. Trauma to adjacent tissues should be avoided by gentle, accurate clamping of the vessel alone, where possible.

A well applied ligature is simple and preferable to suturing. Suturing may be used where trauma is great and a large area bleeds copiously. We have found suturing seldom necessary.

Secondary Hemorrhage: In addition to the above measure, secondary bleeding may require other special measures.

Rest in bed and thorough sedation by morphia is usually sufficient to stop bleeding. An ice collar may be used if comforting to the patient, and vitamin K should be given in larger doses.

If the bleeding continues, it will be necessary to remove the clot, under which a vessel continues to ooze. This is easily accomplished by ring, sponge forceps, and may alone be sufficient to stop bleeding. It may be necessary to touch the bleeding area with a solution of thrombin or adrenalin, silver nitrate 50 per cent, Monsell's solution, tannic acid, chromic acid or other caustics.

To inject a small amount of novocaine or adrenalin about the site of bleeding is a most useful and painless method of controlling hemorrhage.

Occasionally these simple measures fail, and it becomes necessary to put a ligature or suture about the offending vessel. We find that 2 per cent pontocaine applied locally or novocaine injected into the floor of the fossa greatly reduces the pain of this procedure. Since the tissue is friable and difficult to tie, we prefer to use a small atraumatic needled supplied with catgut. So little pain is incurred that it is seldom necessary to give general anesthesia, even to small children. Restraint and a mouth gag are usually necessary to control children, but every effort to gain the patient's confidence and to reassure him is of equal importance.

General supportive treatment such as glucose or proteins

by infusions and transfusions of whole blood or plasma should be used early when much blood is lost.

Management of Tonsillectomy: Discussion of this phase of the subject is limited to the relation of management of tonsillectomy, to the prevention and control of hemorrhage. It will be confined to and based upon the studies presented above. More detailed discussions, such as the studies by Shambaugh or Jones,[9,10] maye be referred to by those interested.

Preoperative Management: Patients who have had recent acute infections should not be subjected to tonsillectomy for from two to four weeks after recovery. In addition, it may be wise to give these patients two days of treatment with suitable antibiotics immediately preceding the operation.

If the history suggests bleeding, a complete blood study should be made. Vitamin K in doses of 5 mg. for children and 10 mg. for adults should be given before meals and at bedtime, for one or two days preoperatively.

Sedation with barbiturates and atropine prevents psychological shock in children, and morphia may be added for adults. It should be remembered, though, that barbiturates may prolong the prothrombin time and that vitamin K will prevent this.

Operative Management: The type of anesthesia should be that safest in the hands of a given anesthetist. It should be given over the shortest period of time consistent with careful surgery and complete hemostasis.

The author has found that removal of the adenoids first has been the greatest single factor in reducing the trauma to the posterior pillar. A sharp adenotome should be used with gentleness and stripping of the pharyngeal mucosa should be avoided. While it is freely admitted that the use of the adenoid curette is subject to criticism, one often finds it indispensable to a thorough job, providing care and gentleness are used.

Gentle palpation with the forefinger will reveal tags of

infected lymphoid tissue remaining which tend to bleed if not removed.

String sponges or gentle pressure with a sponge in the nasopharynx should be used to control bleeding. Sponges, wet with a solution of thrombin, usually hasten hemostasis. By whatever means necessary, hemostasis should be complete before the patient leaves the table.

Regarding the method of removing the tonsils, one cannot emphasize too strongly that the method of choice is the one which the surgeon can use most quickly, thoroughly and with the least trauma. Many tonsils are poorly adapted to the use of the Beck type instrument, in which case dissection may be the method of choice. In our studies, we feel that less delayed bleeding follows the use of the Beck type of instrument, probably due to diminished trauma. The Beck instrument should be followed by the snare to remove the tissue at the lower pole of the tonsil fossa.

Vitamin K in doses of 5 mg. for children and 10 mg. for adults is given with or without ascorbic acid before meals and at bedtime for 10 days after the operation.

Vitamin K is often given intramuscularly and helps control persistent oozing in the fossa while the patient is on the table.

Aspirin gr. V, or Aspergum, is given before meals and at bedtime if required, but patients are cautioned not to use it in excess.

Sulfonamides and penicillin are used freely, if infection is anticipated, and sulfathiazole chewing gum may be especially useful in these cases.

A few concisely written instructions are provided for each patient to guide his convalescence. They may be varied to suit a given case, and we submit the one used by us, as it is brief and has proven satisfactory. These prepared instructions save much time and explanation to patients.

By adhering to these few simple measures, we have been able to reduce the incidence of postoperative tonsil hemorrhage on an average of 5.3 per cent in the years of 1939 to 1944, to

TABLE 6. POSTOPERATIVE ORDERS FOR TONSIL PATIENTS.

Rest in bed three or four days. Purgative (mild) tonight. Aspirin or Aspergum in as small amounts as possible to keep reasonably comfortable. Before meals and at bedtime should be enough. Aspirin promotes hemorrhage.

Soft and liquid diet few days—anything can swallow. Insist on nourishment being taken. Take vitamin K tablets as prescribed.

In case of bleeding, take more vitamin K. Rest quietly. Be calm and come to the hospital.

an average of 0.88 per cent for delayed, and 1.7 per cent for all bleeding in the years of 1946 and 1947.

SUMMARY.

1. A brief resumé of the physiology and dynamics of hemostasis is given.

2. A study of 3,260 cases of tonsillectomy is presented to emphasize certain etiological factors of postoperative hemorrhage.

3. A brief survey of the diagnosis and management of hemorrhage is discussed.

4. A general plan of management of the operation of tonsillectomy is suggested for the reduction of the postoperative tonsil bleeding.

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THE EFFECT OF THE L-EPHEDRINE SALT OF PENICILLIN G (TERSAVIN*) ON THE BACTERIAL FLORA OF THE NASAL MUCOSA.†

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In an interesting paper by Everett,[1] it has been shown that sodium sulfathiazole, particularly in combination with dl-desoxyephedrine as a vasoconstrictor, was superior to penicillin in the treatment of infected sinuses. This is surprising because of the superior antibacterial activity of penicillin towards the Gram-positive and Gram-negative cocci, which in Everett's investigations were also found to be the most common causative agents of sinus infections. It suggests that the presence of the vasoconstrictor plays an important rôle in the successful treatment of inflammatory infectious processes of the nose. Mixtures of penicillin and vasoconstrictors are apparently widely used and of satisfactory activity.[2] For that reason, a series of investigations was recently carried out in which the antibacterial effects of an l-ephedrine salt of penicillin G were examined both clinically[3] and experimentally.[4]

The l-ephedrine salt of penicillin G, synthesized by Dr. M. W. Goldberg and Mr. S. Teitel, of the Roche Chemical Laboratories, is a compound which combines in one molecule the vasoconstrictory properties of ephedrine and the antibacterial activity of penicillin G. Studies on the pharmacology and chemotherapeutic effects of this compound have been published elsewhere.[4] These investigations have shown that, due to the presence of the vasoconstrictor, the absorption from the site of administration was delayed and consequently the

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topical prophylactic antistreptococcal activity was superior to that of other water-soluble penicillin salts.

It was the observation on the topical activity of Tersavin that suggested the usefulness of this penicillin derivative for topical administration on infected tissues and surfaces. The favorable physical properties of this compound, namely: the high solubility, the absence of disturbing color and the innocuousness for tissues, were considered additional factors which encouraged the use of this material on mucus surfaces inhabited by a normal and occasionally pathologic flora. As an easily available test object for the determination of the activity of this penicillin salt on a bacterial infected mucus surface, the nasal mucosa was selected. The studies were conducted on volunteers with a supposedly normal nasal flora (*i.e.*, people without actual acute or chronic nasal disturbances), as well as on patients of an ear, nose and throat clinic.

MATERIALS AND METHODS.

Two tablets of Tersavin, containing 30,000 units penicillin/tablet, were dissolved in 15 ml of distilled water or saline so that a concentration of 4,000 units penicillin/ml was obtained. With the cooperation of Dr. Reginald Everett, St. Luke's Hospital, New York, N. Y., nasal swabs were obtained from patients immediately before treatment and streaked on blood agar plates containing 1 mg penicillinase/ml. Twenty minims of the Tersavin solution were then instilled into the nostril from which the initial swab had been obtained. At various intervals after treatment, swabs were taken and streaked on penicillinase (1 mg/ml) blood agar plates so that any residual penicillin would be inactivated.

Grubb and Puetzer's[5] criticism of the swab technique, namely, that the bacterial flora picked up by the swab at the vestibule of the nares might have insufficient contact with the penicillin is indeed justified. In our use of the swab method, the decrease in the flora after Tersavin therapy was so striking that even this interference could be disregarded; therefore, the swab technique was used throughout our experiments.

EXPERIMENTAL RESULTS.

The flora obtained in the present cases were usually *Staphylococcus aureus* and *Staphylococcus albus*. In a few patients, hemolytic streptococci were isolated. The initial cultures, which were taken before treatment with Tersavin, showed innumerable colonies in the majority of cases. Less than 500 colonies could be counted in those cases where reduction in the nasal flora was seen. Frequently a reduction to less than 100 colonies and occasionally no visible growth was observed in these experiments.

The per cent of cases which showed a reduction in the nasal flora 15 minutes to four hours after one treatment, three hours after three treatments at two-hour intervals, and three to four hours after three treatments on one day and the fourth treatment on the following morning are given in Table 1. In all cases, a minimum of 70 per cent of those treated showed a reduction in the nasal flora.

TABLE 1. EFFECT OF TERSAVIN ON NORMAL AND PATHOLOGIC NASAL FLORA.

Subculture on Blood Agar Plate + 1 Mg/Ml Penicillinase.

No. of Cases	No. of Treatments	Interval	No. of Patients Showing Reduction in Nasal Flora	% Patients Showing Reduction in Nasal Flora
13	1	15 min.	9	70
6	1	1 hour	6	100
3	1	4 hours	2	66
20	3	3 hours	15	75
12	4	3-4 hours	11	92

In order to use the more sensitive method of liquid medium for the question of the reduction of nasal flora, some of the swabs taken three to four hours after treatment were put into broth and incubated. A striking example of the results obtained is given in Fig. 1. The tube, 133A, which is perfectly clear, indicates the inoculation of the swab after therapy with Tersavin, while 133B, which is highly turbid, was taken before

the administration of Tersavin. The swabs, put into the test tubes, are still visible in the photograph.

Even after longer intervals between the last treatment and the taking of a final culture, a significant reduction in the nasal flora may be seen. Three cases in which the subculture period ranged from 11 to 20 hours after the last treatment of repeated doses showed a considerable reduction. Fig. 2 is from a case of a known carrier of hemolytic *Staphylococcus*

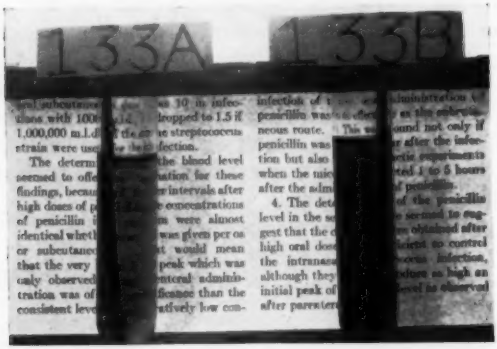

Fig. 1. Growth in broth of nasal swabs taken before and three to four hours after treatment with Tersavin.

aureus who suffered from relapsing boils of the nares. After the initial cultures, the patient instilled 20 minims of the Tersavin solution two to four times daily in both nostrils for four days. On the morning of the fifth day, about 20 hours after the last administration of Tersavin, swabs were again taken from both nostrils. The number of colonies were innumerable before treatment, but after therapy were reduced to 340 colonies for the right and 92 colonies for the left nostril.

These results clearly demonstrate the fact that local Tersavin therapy is able to reduce the bacterial flora on a mucus surface; moreover, the reduction of the nasal flora lasted for a period far beyond that time within which penicillin might be expected to remain in living tissue. This observation was

not surprising to us since an earlier publication by Grunberg, Schnitzer and Unger[6] had shown that, although no detectable penicillin could be observed in tissues two hours after a topical penicillin treatment, a sufficient amount was adsorbed on the bacteria to exert an effect for a considerably longer period of time.

In an attempt to further analyze these findings, Grunberg and Unger[7] employed Fleming's gutter plate method, in order

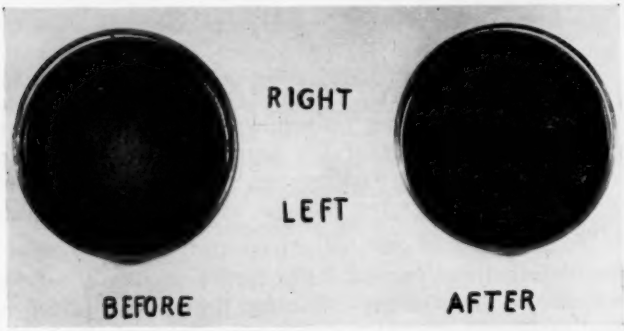

Fig. 2. Nasal flora before and 20 hours after four days' treatment with Tersavin.

to show that pathogenic organisms, in this case *Streptococcus hemolyticus*, showed an increased sensitivity to extremely small amounts of penicillin. It was assumed that this was due to an additive effect of the penicillin which diffused into the agar plus that residual penicillin specifically adsorbed to the surface of the organisms. It was, therefore, attempted to demonstrate a similar increased sensitivity of bacteria towards penicillin after treatment of the nasal mucosa with Tersavin by a series of experiments in which swab cultures of the treated mucosa were plated on blood agar plates containing a noninhibitory dose of penicillin. A group of volunteers were, therefore, first examined in order to find out which concentration of penicillin in the blood agar allowed full growth of bacteria and which one was sufficient to inhibit growth completely. The results are given in Table 2.

TABLE 2. SENSITIVITY OF THE NASAL FLORA TO PENCILLIN G INCORPORATED INTO BLOOD AGAR PLATES.

Volunteer Initials	Penicillin Concentration in the Agar (mcg/ml)			
	0.0006	0.006	0.06	0.3
D. R.	+++(a)	++	5 col.	0
B. L.	—	—	0	0
A. D.	+++	+++	0	0
M. D.	—	—	0	0
E. G.	++	++	2 col.	0
D. K.	+++	60 col.	1 col.	0
R. S.	+++	+++	6 col.	4 col.
W. H.	+++	+++	—	—

(a) +++ = heavy growth of innumerable colonies.
++ = lighter growth, colonies still innumerable.
— = not tested.

It may be seen from Table 2 that in the majority of cases a concentration of 0.006 mcg penicillin/ml or less did not interfere with heavy growth of the nasal staphylococcus flora, while concentrations of 0.06 mcg/ml and more allowed only the development of very few colonies; in most cases there was no growth at all.

Considering these results, 0.003 mcg penicillin G/ml was chosen as the noninhibitory dose for demonstrating the increased sensitivity of the nasal flora after Tersavin treatment. The results are given in Table 3.

TABLE 3. GROWTH OF NASAL FLORA ON BLOOD AGAR CONTAINING PENCILLIN G 0.003 MCG/ML BEFORE AND AFTER A SINGLE ADMINISTRATION OF TERSAVIN (4,000 U/ML).

Exp. No.	Volunteer Initials	Number of Colonies				
		Before	After 8	16	24	40 Hours
E 184	R. S.	inn.(a)	87	—	300	—
	D. K.	inn.	20	—	40	—
E 183	R. S.	650	—	76	45	400
	A. D.	900	—	425	53	210

(a) inn. = innumerable.

It is evident from these experiments that after 24 hours, and to a certain degree after 40 hours, only a small fraction of the surviving nasal flora was able to grow in the presence of an noninhibitory concentration of penicillin which allowed

good growth of the nasal flora before treatment. These experiments substantiate the fact that the growth of staphylococci from the nasal mucosa after treatment with Tersavin is inhibited by very small concentrations of penicillin incorporated into the agar. The concentrations *per se* are not sufficient to influence the growth of the nasal flora without pretreatment with Tersavin.

The findings also appear to be interesting from the point of view of the possible development of a specific drug resistance induced by the use of a topical treatment of a penicillin salt. It has recently been shown that chemotherapeutic agents, particularly streptocomycin[8] and to a lesser degree penicillin,[9] selectively affect individual bacteria of high sensitivity, while the more resistant individuals of the same population may survive and give rise to the development of resistant strains. Such a selective survival of micro-organisms of abnormally increased resistance has not been observed so far either in our experimental work on artificial infections of mice or in our work with the flora of the nasal mucosa. This was shown by the use of culture medium containing high concentrations (0.06 mcg/ml) of pencillin which in no case allowed the growth of organisms after the administration of Tersavin. The development of drug resistance *in vivo* seems, therefore, to follow other rules than those suggested by *in vitro* experiments. This is also shown in older studies by Schnitzer[10] and in the more recent investigations by Gezon and Collins.[11]

DISCUSSION.

The studies presented in this paper form a confirmation of previous experimental studies in infected tissues of animals and demonstrate that the topical administration of Tersavin significantly decreases the bacterial flora of the normal and diseased nasal mucosa for a considerable length of time. Evidence is also presented that the antibacterial effect of the treatment lasts for a longer period of time than penicillin can be expected to be present in a detectable concentration. An explanation for this phenomenon was attempted by demon-

strating that the surviving individuals of the bacterial population showed an increased sensitivity towards penicillin.

We are aware of the fact that these observations, which have been partly carried out in healthy volunteers, might not have an immediate significance for clinical problems. The fact that it is possible by simple instillation of a vasoconstrictory ephedrine salt of penicillin to reduce the nasal flora might, however, have implications of a clinical therapeutic nature in acute or chronic diseases of the nose. The results seem to indicate that Tersavin might be of value in other infectious processes of the nasal accessory sinuses where a direct influence on the viability of pathogenic micro-organisms is more to be desired than might be the case with the physiological flora of the mucus surface of the nose.

SUMMARY.

Experimental data are submitted to show that Tersavin, the l-ephedrine salt of penicillin G, significantly decreases the bacterial flora of the normal and diseased nasal mucosa for a considerable length of time. In addition, the flora exposed to Tersavin treatment develops an increased sensitivity towards noninhibitory doses of penicillin. The results obtained on the experimental model of the nasal flora might indicate a similar therapeutically valuable effect on the pathological flora of infected nasal accessory sinuses.

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CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

On Nov. 12, 13 and 14, 1948, the Central Illinois Society of Ophthalmology and Otolaryngology held their eleventh meeting at the Abraham Lincoln Hotel in Springfield, Ill. Dr. F. Bruce Fralick, professor of ophthalmology at the University of Michigan, spoke on "Surgical Anatomy of Operations for Glaucoma" and "Diseases of the Tear Duct." Dr. F. L. Lederer, professor and head of the Department of Otoloryngology, University of Illinois, discussed "Modern Approaches to the Prevention and Treatment of Defective Hearing" and "Malignancy in Its Relationship to Nasal Obstruction and Hoarseness." Dr. L. W. Roth, Belleville, Ill., gave a paper on the "O'Connor Cinch Operation," and Dr. D. K. Judd, of Kankakee, Ill., discussed "Malignancies of the Paranasal Sinuses." Thomas W. Samuels, an attorney from Decatur, Ill., gave a delightful talk on "A Lawyer Looks at the Medical Profession." The following officers were elected for 1949: President, Dr. Clifton S. Turner, Peoria, Ill.; President-elect, Dr. Harold Watkins, Bloomington, Ill.; Vice-President, Dr. Meredith Ostrom, Rock Island, Ill.; Secretary-Treasurer, Dr. Philip R. McGrath, Peoria, Ill.

CLINICAL STUDY OF VONECIDIN.*†

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The therapeutic aims of local medication in the management of rhinological conditions are to reduce congestion of the nasal mucosa, to promote or restore ciliary function and to control secondary bacterial invasion.

The most desirable and widely useful single drug for accomplishing the first of these aims is the nasal decongestant. The ideal medication of this type must provide effective and prolonged vasoconstriction without disturbing the normal physiology of the nose; it should be nonirritating and devoid of local and systemic side-effects; and it should not cause secondary or rebound congestion and turgescence of the nasal tissues.

Vonedrine solution has been shown, pharmacologically and in clinical rhinological practice, to possess certain advantages over nasal decongestants in common usage.

Chemically, Vonedrine is phenylpropylmethylamine, a secondary amine. It forms salts readily with mineral acids which are stable and do not decompose on storage under ordinary conditions of exposure. The hydrochloride is a white crystalline salt with a melting point of 114° C. It is very soluble in water and alcohol, slightly soluble in acetone, and insoluble in benzene, chloroform and ether. The solution for intranasal use is isotonic.

Vonedrine exerts its essential therapeutic action on the deep vascular plexus, which is the objective in decongestant therapy. This network of blood vessels controls the thickness of the tissues over the turbinates, and by decreasing the blood

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through vasoconstriction the swollen turbinates shrink and the capacity of the airway is increased. Constriction of the superficial blood vessels, on the other hand, would result only in blanching of the mucosa, causing a local ischemia which obscures the actual degree of inflammatory mucosal reaction and disturbs nasal physiology.

Because of the characteristic action of Vonedrine—effective decongestion without blanching—topical application or inhalation into the nose does not produce stinging or burning. The onset of vasoconstriction is not quite so rapid as that of certain other nasal decongestants but the degree of congestion is equally as great and the period of decongestion is of longer duration. The use of Vonedrine is not followed by rebound secondary congestion or turgescence. The initial vasoconstricting action of Vonedrine is more physiological and not so intense as is that of many other decongestants, and since the secondary congestion which usually attends the use of nasal vasoconstrictors is directly proportional to the intensity of the primary effect, there is little likelihood of local secondary congestion or undesirable systemic side-actions.

The pharmacological and toxic effects of Vonedrine were studied and compared with those of l-ephedrine and amphetamine.[1] The effect of Vonedrine on the cardiovascular system and the bronchioles is very similar, both quantitatively and qualitatively, to that of amphetamine; however, it produces very little, if any, central stimulation in the experimental animal. Warren and Werner,[2] in a comparative study of the central stimulating action of seven commercial vasopressor amines used as nasal decongestants, found that Vonedrine had no effect at the lowest dose level and only slight effect at the highest level. The toxicity of Vonedrine is of the same order as l-ephedrine and about one-half that of amphetamine.[1]

Vonedrine solution was originally supplied for clinical investigation in 0.5 per cent concentration of Vonedrine Levulinate. Baumgardner and co-workers,[3] based on their study of 150 rhinological patients, reported this to be an effective nasal

decongestant both by topical application and inhalation, and its action was unaccompanied by local or systemic side-actions.

Based on actual observation of the tissues, the degree of decongestion provided by the 0.5 per cent solution was as good as that of other vasoconstrictors; however, the onset of action was more gradual, and this, together with the absence of stinging or irritation on application, made evaluation of subjective response to this nasal medication somewhat difficult.

In view of the fact that Vonedrine has such a low toxicity and wide margin of safety, it was felt that the strength could be increased quite materially. Further investigation on the part of the manufacturers resulted in the development of a 2.8 per cent solution of Vonedrine Hydrochloride with Ceepryn (cetylpyridinium) Chloride, a detergent germicide. This agent has a wetting action and seems to facilitate spreading and intimate contact with the mucosal epithelium. Its germicidal action prevents bottle contamination on repeated intranasal use of the dropper. This solution is isotonic and seems to provide a better detergent and decongestant action, the onset of which is rapid. A great improvement in the new solution is that it produces a rather refreshing sensation when applied.

In my own experience with this 2.8 per cent solution I have found it to be very well tolerated. I have used it as nasal packs and as an additional spray. It alone was quite sufficient to produce the desired shrinking effect. In no case has nervousness, jitteryness or rise in blood pressure been noted following the repeated use of this decongestant. This is a distinct advantage over ephedrine solutions.

Most vasoconstrictors do not have an actual damaging effect upon ciliary activity in the concentrations usually employed. They may, however, cause a temporary inhibition of ciliary movement. There is some controversy in the medical literature in regard to whether this temporary inhibiting effect of vasoconstrictors upon ciliated mucous membrane in the upper respiratory tract is desirable.

The lining membrane of the entire respiratory tract, including the sinuses, is covered by an overlying mucus blanket which is propelled, by ciliary movement, downward and backward toward the nasopharynx where it is either swallowed or coughed up. The function, then, of cilia is mechanical; that is, they move substances on them. In the respiratory passages, by ciliary activity, dust, foreign particles of various sorts and harmful bacteria, together with the film of mucus which is constantly replaced, are carried away; therefore, any interference with ciliary movement may tend to cause at least temporary obstruction of the air passages.

On the other hand, a temporary inhibition of ciliary movement may be necessary for good nasal medication; indeed, it might possibly be the only way to obtain effective intranasal medication with antibiotics in the presence of infection since the antibiotic must be retained in the nasal chambers and passages long enough to act on sensitive organisms.

Some time ago, nasal decongestants with sulfonamides were introduced, but they proved to be somewhat harmful to the nasal mucosa and their use has been largely abandoned. More recently, an antibiotic has been used for its antibacterial action. It is somewhat difficult to appraise the value of such an agent in nasal medication; however, if the substance is not harmful and has a wide bacterial spectrum for the pathogenic organisms ordinarily found in the nasopharynx, its use would seem justified.

Taylor and Foter[4] conducted *in vitro* studies of the antibacterial action of Vonedrine solution, to which was added a chemically modified antibiotic, Methacidin (methylol gramicidin) in 1:10,000 concentration. This solution is called Vonecidin. They found that gramicidin, the more active of the two components of tyrothricin, when reacted with formaldehyde to produce methylol gramicidin, was rendered more soluble and less toxic. It possesses little, if any, hemolytic action. Tyrocidin, which represents 60 to 80 per cent of tyrothricin, is quite hemolytic and practically inactive *in vivo* since its action is greatly decreased by small amounts of albumin.

The antibacterial action of Vonecidin was compared to two similar preparations containing tyrothricin. Tests were made in the presence of 10 per cent serum. It was found that Vonecidin had a somewhat better effect, and this was attributed to the synergistic action of the detergent germicide, Ceepryn Chloride, and the chemically modified antibiotic, Methacidin.

The self-sterilizing properties of Vonecidin were studied by Taylor and Foter. They contaminated the solution with individual organisms and with nasal secretions. A saline solution was used as a control. After 10 and 60 minutes, it was found that bacteria and fungi were practically eliminated in the Vonecidin, whereas they were thriving in large numbers in the saline controls.

The proved clinical efficacy of Vonedrine and the low toxicity and high antibacterial action of Methacidin indicated Vonecidin to be a safe and effective intranasal medication.

For the past year, this preparation has been used in 750(?) patients as adjunctive treatment for acute nasopharyngitis, acute colds, and maxillary, frontal, ethmoid and sphenoid sinusitis. The mode of use was by nasal packs and spray, after which patients received infrared heat for 15 to 20 minutes. Average duration of treatment varied from three to 10 days. A number of patients had repeated treatments on recurrence of the condition.

In all cases there was relief of congestion and the condition seemed to clear more rapidly than when the nasal solution without the antibacterial agent was used. No patient complained of smarting and burning, and objectively there was no irritation. No objective signs of tissue irritation were noted. Patients preferred this medication to that formerly employed. There was no nervousness nor increase in pulse rate or blood pressure in any of this series.

Occasionally, Vonecidin was used as a lavage of an acute maxillary sinusitis. The solution was introduced into the sinuses, and then withdrawn. After removal of the solution

and discharges, 5 cc. of Vonecidin were injected into each sinus. There was no complaint of smarting or burning.

Recently, Seydell and McKnight[5] reported a disturbance of olfaction resulting from the intranasal use of tyrothricin, evidenced as parosmia and anosmia, which persisted over a period of months. We have noted no disturbance in olfaction from Vonecidin. This may be due to the chemically modified antibiotic, Methacidin, present in Vonecidin, which is less toxic than tyrothricin. It also does not contain the hemolytic component of tyrothricin; namely, tyrocidin.

Summary: Vonecidin, an intrasanal solution containing a decongestant, a detergent germicide and a chemically modified antibiotic, has been used in 750 patients suffering with acute nasopharyngitis, acute colds and sinusitis.

All patients were relieved. There was no burning or irritation or secondary congestion, and in no case was there any nervousness or pressor action from the vasoconstrictor. There apparently was quicker clearing of the condition than when the nasal solution without the antibiotic agent was used.

There was no disturbance in olfaction.

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THE CENTRAL STIMULANT ACTION OF SOME COMMERCIAL NOSE DROP PREPARATIONS.*

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An essential ingredient of most nose drop preparations is a pressor amine which induces shrinkage of the nasal passages by a local vasoconstrictor effect. Apart from this effect, many of the commonly used pressor agents cause stimulation of the central nervous system which, although beneficial in numerous clinical conditions, is a disadvantage in nose drops and in other preparations employed for a purely local effect. A search of the literature failed to reveal any reports on the comparative central stimulant action of different commercial nose drop preparations, and it was with this study in mind that the present work was undertaken. Warren and Werner (1945) studied the activity of rats following subcutaneous administration of seven pressor amines given in doses equal to fractional parts of the LD50. Our work differs from theirs in that the nose drops were added intranasally at repeated intervals. This method of administering nose drops for comparative testing, although open to the criticism that it is less accurate than parenteral injection, so far as dosage is concerned, is more logical since it parallels exactly the route by which the drops are taken therapeutically.

In addition to the above, studies were also made on the central stimulation of the commercial nose drop preparations following their intraperitoneal injection.

METHODS.

a. Central Stimulation: The technique employed for record-

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ing central stimulation was essentially that of Schulte and co-workers (1941), with one important modification. It had been our experience that the sensitivity of the work adders varied with the setting of the adjustment screws into the axle, owing to differences of pressure, and it was possible that their sensitivity varied from day to day, or even during the course of an experiment. To overcome this difficulty the following changes were made: the adjustment screws were eliminated. two ball bearings were inserted over the axle, and recessed into the wheel of the work adder, and two thrust bearings were placed on either side of the movable lever. With these improvements the instruments were made more sensitive and their performance more constant.

b. Animals: Adult male and female rats, fed Purina laboratory chow supplemented with greens in season, were employed in these experiments. All tests were made on four groups of 10 rats each.

c. Procedure: The test chamber was fitted with 10 cages so that 10 animals were treated at one time, five of which were given the test solution and five the control solution. On the following day or, in some instances, two or three days later, the experiment was repeated with the same animals in the same cages, but with the solutions reversed. By this arrangement a "crossover" test was performed and values for the difference between the effect of the test and control solutions were calculated. The volume of solution administered to each rat was 0.7 cc. and this was given either as a single injection (intraperitoneally), or as seven divided doses of 0.1 cc. each (intranasally) given at 10-minute intervals, since the rats did not accept more than 0.1 cc. applications without undue loss of the material. Following drug administration, the animals were put into the test chamber and allowed a 15-minute adjustment period, after which the kymograph was started and activity recorded for six hours. The average activity of at least 10 animals was recorded for each test, although in some tests 20 and 30 animals were used.

Most of the experiments were carried out at a temperature

of 27° to 29° C. In very hot weather the air in the test chamber was cooled by passing it through a coil in ice but, even so, the temperature on two occasions increased during a test from an initial temperature of 29° to 33° C. at the end of the experiment.

Apart from the one exception noted, the nose drop preparations studied in these investigations were purchased on the open market. These were: Nose drop A (0.3 per cent ephedrine in mineral oil); Nose drop B (0.5 per cent ephedrine in mineral oil); Privine (0.1 per cent 2[α-naphthylmethyl] imidazoline hydrochloride]; Tuamine (2 per cent dl-2 aminoheptane sulfate); Neo-Synephrine (1 per cent 1[m-hydroxyphenyl]-2-methylaminoethanol hydrochloride). Nose drop C, an aqueous isotonic buffered solution containing 0.5 per cent ephedrine sulfate, 0.04 per cent cetyl trimethyl ammonium bromide and 0.25 per cent chlorobutanol, was prepared in the laboratory. The control solution for the aqueous preparations was 0.9 per cent saline and for the oily preparations light mineral oil. These were administered in a manner and volume similar to that used for the experimental animals.

RESULTS.

a. Intranasal Administration: A summary of the results of the tests on intranasal administration of nose drops is given in Table 1, with two examples of the crossover test in Table 2. It is to be noted that Privine, at the dosage used, caused definite central stimulation, whereas none of the other nose drop preparations did. That Neo-Synephrine and Tuamine were without effect is not surprising, as these agents are well known to be weak central stimulants, but that the three preparations containing ephedrine should prove to be without action was of considerable interest.

b. Intraperitoneal Administration: Since Privine had proved stimulating when given intranasally, but not nose drops containing ephedrine, it was decided to study the action of these agents when injected intraperitoneally to see if the route of administration had a bearing on the result. It was

TABLE 1. THE TOTAL ACTIVITY OF RATS FOLLOWING THE INTRANASAL ADMINISTRATION OF 0.7 CC. OF VARIOUS COMMERCIAL NOSE DROP PREPARATIONS AND CONTROL SOLUTIONS (CROSSOVER TESTS).

Exper. No.	No. of Rats Used	Revolutions of Work Adder Exper. and Control Animals		Ratio of Revolutions Exper./Control	"t" Value and Significane	
1	20	Privine (0.1%)	172	1.39	2.91	H. S.*
	20	Saline	123			
2	30	Nose drop A (ephed. 0.3%)	232	0.92	0.48	N. S.†
	30	Mineral oil	251			
3	30	Nose drop B (ephed. 0.5%)	243	1.15	1.02	N. S.
	30	Mineral oil	222			
4	30	Nose drop C (ephed. SO_4 0.5%)	278	1.19	1.82	N. S.
	30	Saline	233			
5	29	Neo-Synephrine (1%)	202	1.02	0.21	N. S.
	29	Saline	197			
6	20	Tuamine (2%)	107	0.87	1.01	N. S.
	20	Saline	123			

*H. S. = highly significant. †N. S. = not significant. —

TABLE 2.† CROSSOVER TEST ON 20 RATS GIVEN PRIVINE AND SALINE, AND 30 RATS GIVEN NOSE DROP A AND MINERAL OIL. ANIMALS STUDIED IN GROUPS OF 10.

No. of Animal	Rev. of Work Adder Privine	Rev. of Work Adder Saline	Difference† P-S	Rev. of Work Adder Nose Drop A	Rev. of Work Adder Min. Oil	Difference† A-M. O.
1	6	4	+ 2	3	4	— 1
2	12	6	+ 6	15	8	+ 7
3	18	18	0	2	1	+ 1
4	9	10	— 1	45	33	+12
5	5	5	0	4	2	+ 2
6	9	4	+ 5	0	0	0
7	5	2	+ 3	0	1	— 1
8	11	12	— 1	24	26	— 2
9	7	6	+ 1	2	2	0
10	18	12	+ 6	3	5	— 2
11	3	1	+ 2	2	4	— 2
12	11	6	+ 5	3	8	— 5
13	2	1	+ 1	0	1	— 1
14	26	11	+15	12	17	— 5
15	4	2	+ 2	11	8	+ 3
16	0	0	0	1	1	0
17	1	1	0	1	1	0
18	20	17	+ 3	6	12	— 6
19	3	1	+ 2	2	2	0
20	2	4	— 2	3	3	0
21				4	3	+ 1
22				9	2	+ 7
23				4	4	0
24				1	3	— 2
25				5	7	— 2
26				5	37	—32
27				37	35	+ 2
28				8	9	— 1
29				8	7	+ 1
30				12	5	+ 7
			+49			—19

$\bar{x} = \frac{49}{20} = 2.45$ $\quad S^2 = 14.16$ $\quad S = 3.76$ $\quad S\bar{x} = .841$

$t = \frac{2.45-0}{.841} = 2.91$

$\bar{x} = \frac{19}{30} = .63$ $\quad S^2 = 51.063$ $\quad S = 7.15$ $\quad S\bar{x} = 1.32$

$t = \frac{.63-0}{1.32} = .48$

*Difference: P-S = Privine — Saline.
A-M. O. = Nose drop A — Mineral Oil.

†Student's "t" test (Statistical Methods, G. W. Snedecor, 1946, p. 44) where "t" = mean of differences between two sets of observations — expected difference) ÷ (standard deviation ÷ $\sqrt{\text{number animals}}$) was employed to test the significance of the difference between the number of revolutions produced by the nose drops and the control material. A "t" value greater than 2.85 means that such a difference should occur not more than once in 100 times by chance when 20 animals are used and hence is highly significant. When 30 animals are used, a "t" value less than 2.04 means that the observed difference might arise by chance and is, therefore, not significant.

TABLE 3. THE TOTAL ACTIVITY OF RATS GIVEN NOSE DROP PREPARATIONS AND CONTROL SOLUTIONS INTRAPERITONEALLY (CROSSOVER TESTS).

Exper. No.	No. of Rats Used	Total Revolutions of Work Adder		Ratio of Revolutions Exper./Control	"t" Value and Significance	
1	10	Privine (0.1%)	1867*	18.67	3.71	H. S.
	10	Saline	67			
2	30	Nose drop A (0.3% ephed.)	457	1.65	4.08	H. S.
	30	Mineral Oil	277			
3	30	Nose drop C (0.5% ephed. SO_4)	1026	2.36	6.52	H. S.
	30	Saline	435			

*Three rats died on this dose of Privine, so that the number of revolutions recorded errs on the low side.

felt that the same approximate order of activity might hold regardless of quantitative differences.

It will be noted from Table 3 that the two nose drop preparations tested containing ephedrine caused central stimulation, and of these the aqueous one proved much more stimulating than the oily one, as would be expected. Privine, however, was more centrally stimulating than even the aqueous ephedrine nose drop.

DISCUSSION.

The results of these tests indicate: That Privine, given intranasally or intraperitoneally, is more centrally stimulating than larger doses of ephedrine; that certain nose drops —*e.g.*, Privine — if given repeatedly by the nasal route, will cause central stimulation; that ephedrine in aqueous or oily phase, intranasally, does not cause stimulation in the doses examined. These three points will be discussed, in this order, below.

1. Warren and Werner (1945) found that when the four above tested pressor amines were studied by subcutaneous injection in the rat, in doses which were fractional parts of the LD50, their order of activity was as follows: ephedrine> Privine>Tuamine>Neo-Synephrine. They used doses that were 5, 10 and 20 per cent of the LD50 values. At the 10 per cent level this would mean that their animals received the

TABLE 4. A COMPARISON OF THE APPROXIMATE AMOUNTS OF PRESSOR SUBSTANCES GIVEN INTRANASALLY (OR INTRAPERITONEALLY) and SUBCUTANEOUSLY. (DATA FOR THE LATTER TAKEN FROM PAPER BY WARRREN AND WENER.)

Pressor Agent	LD50* Mg/Kg	10% of LD50 Mg/Kg	Amts. Given in Present Test Mg/Kg†
Ephedrine	800	80	14‡
Privine	420	42	2.8
Tuamine	130	13	56
Neo-Synephrine	28	2.8	28

*All compounds were tested as the hydrochloride salts except Tuamine, which was tested as the sulfate.

†Calculations based on 0.7 cc./250 gm. rat; i.e., 2.8 cc. of nose drop preparation per Kg.

‡Using aqueous nose drop containing 0.5% ephedrine sulfate.

amounts listed in Table 4. For purposes of comparison, the quantities given intranasally or intraperitoneally to our rats are recorded in the last column of the same table.

It is evident from the results given in Table 1 and 3 that nose drops containing Privine proved to be more centrally stimulating than those containing ephedrine, even though the dose of ephedrine was greater than Privine. This relationship was found regardless of whether the nose drops were given intranasally or intraperitoneally. The aqueous nose drops contained 0.5 per cent ephedrine sulfate, whereas Privine nose drops contained 0.1 per cent Privine hydrochloride. In milligrams per kilogram this is equivalent to a dose of 14 mg/kg for ephedrine sulfate and 2.8 mg/kg for Privine hydrochloride. Warren and Werner (1945) found that ephedrine was more stimulating than Privine when injected subcutaneously. This difference in order of activity may be due to the different routes of administration used and/or the fact that our preparations were commercial products with other substances present, and that these substances modified the absorption of the active pressor agents.

The dose of Privine used in the present study, when considered in relation to the LD50 values, was proportionately less than that used for the other pressor amines and, on a weight basis, therefore, Privine was the most active of all agents tested.

2. It was found that if repeated doses of 0.1 per cent Privine were given intranasally to rats over a period of time contral stimulation would result. The amounts administered were large — 0.7 cc. for a 250 gm. rat corresponds on the same weight basis to 196 cc. for a 70 kg. man. Actually, the volumes required to cause central stimulation would be somewhat less than this, as administration of nose drops to the rat is attended with some loss. The method was used, however, as it is the route by which the drugs would be taken therapeutically and moreover, for comparative studies, the dosage error would be approximately the same for all test groups.

3. An important finding was that none of the nose drops

tested containing ephedrine (oily nose drops A and B and aqueous nose drop C) proved to be centrally stimulating when given intranasally in spite of the relatively large doses used. Intraperitoneally, both the oily preparation (nose drop A, 0.3 per cent ephedrine) and the aqueous nose drop (nose drop C, 0.5 per cent ephedrine sulfate) were centrally stimulating, the latter being more active than the former. This difference was probably due to a difference in absorption from the two solutions as the dose of ephedrine base was the same in each.

Finally, it is believed important to emphasize that any conclusions that may be drawn from this study apply only to commercial nose drop preparations as tested under the conditions described and no generalizations with regard to the centrally stimulating action of the pure pressor amine is implied.

SUMMARY.

1. Five different commercial nose drop products and one other prepared in the laboratory, each of which contained a pressor amine, were tested for their central stimulant action in the rat following intranasal administration. Privine was the only one found to be active.

2. Privine, oily nose drop A (0.3 per cent ephedrine), and aqueous nose drop C (0.5 per cent ephedrine sulfate) were also tested for their stimulant action following intraperitoneal injection. All were found to be stimulating, with Privine the most effective. Of the two preparations containing ephedrine, the aqueous drops were more stimulating than the oily ones.

3. The results are discussed in relation to those previously reported.

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DR. THOMAS WILLIS (1621-1675).

A Great Seventeenth Century English Anatomist and Clinician Who Anticipated Many Modern Discoveries.

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Dr. Thomas Willis was a contemporary of Dr. Thomas Sydenham and, in his day, a man of far greater renown. With the passing of years, however, a reversal has taken place, and in medical history Sydenham, "the great English Hippocrates," as he is called, has become such a dominating figure of that period that were it not for certain eponyms which have survived, the name and fame of Willis would be almost completely obscured.

We do not hear much of the Willis nerve, as the accessory nerve has been called, nor of Willis disease, another name for diabetes, but there are two Willis eponyms that are household words in our medical literature.

No one with the least pretense of anatomical knowledge can be unfamiliar with "The Circle of Willis," and surely no otologist could be unfamiliar with the meaning of the expression "Paracusis Willisii."

All deaf persons who have noticed the peculiar phenomenon of hearing better in the midst of noise must share with medical men some curiosity as to the person for whom this symptom is named.

1. The Circle of Willis. This is the name universally bestowed on the network of anastomosing arteries presenting an approximately hexagonal figure at the base of the brain.

It was first described by Willis in his "Cerebri Anatome"

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published in London in 1664, and as most of the illustrations of the work were made by his assistant, Christopher Wren, who was then a medical student at Oxford, the famous architect, it is presumed that the original drawing of this anatomical landmark was by the same hand that later designed St. Paul's Cathedral.

DR. THOMAS WILLIS (1621-1675).

2. The Paracusis of Willis; or Paracusis Willisii. A phenomenon occurring in certain deaf persons, consisting of an ability to hear better in the presence of noise.

The deafness in some cases may be so profound that the individual can ordinarily hear conversation only close to the ear, and yet in the noise of moving railway or subway train will find himself able to carry on conversation with neighboring fellow-passenger with perfect ease.

The presence of this symptom is a valuable diagnostic aid to the otologist. It is a positive indication that he has before him a case not of nerve deafness but one due to an obstructive lesion in the conductive apparatus. The phenomenon, therefore, occurs in those persons in whom the tuning forks tests indicate increased bone conduction, either absolute (prolonged Schwabach) or relative (negative Rinne).

It is considered by many as pathognomonic for stapes fixation, and, therefore, strongly points to otosclerosis in which this condition is common.

We may explain the symptom by the fact that in middle ear or obstructive deafness, there is always an elevation of the lower tone limit, which means that the predominate low tones of railway cars and the like are not so disturbing to the affected individual as to his companions, who customarily raise their voices under these circumstances.

Whether or not, as Politzer suggested, these low note vibrationst have a stimulating effect upon the auditory apparatus in cases of obstructive deafness is a disputed question.

The original case of paracusis reported by Willis was that of an elderly deaf woman who reported that she could always hear very well in the neighborhood of loudly beating drums.

The report of the case was included in "Pharmaceuticae Rationallis" published in 1674.

There is a very special need to recall the life of Thomas Willis and in a spirit of fairness to review his work and character, for he has suffered not only from the neglect of medical historians but also, for some strange reason, from their unjust disparagement.

It has its beginning probably in a slurring allusion by his

first biographer, the quaint chronicler of the era, Anthony á Wood, who insinuated that Willis' reputation as an anatomist was largely due to his exceptionally skilled assistants; and on another occasion when referring to his tremendous income from practice he intimated that this was Willis' chief aim in life. Sir Michael Foster, in his history of physiology, said of Willis, "A love of truth in him was less potent than love of fame; his mind was of the rhetorical sort; he loved words and looked upon an illustration as an argument and when he described an analogy, thought he had found a proof."

In a recent History of Medicine (Mettler, Phil., 1947) an unmistakable bias is evident toward this English physician.

The author seems never to be able to mention his name without adding a slighting remark; indeed, the apparent animosity is carried so far as to include persons who favor him. Sir Charles Bell, the distinguished discoverer of reflex action of nerves, gives credit to Willis for the discovery of the accessory nerve. For doing this, Bell is labeled as one "whose knowledge of anatomical literature was exceeded only by his ambition."

On page 66, we read, "Thomas Willis had one of the most fashionable and lucrative practices in London. He was something of a dandy, and while neither original nor erudite, he was fortunate to secure the help of two men, each about a decade his junior, Richard Lower and Christopher Wren, in the preparation of the work upon which his reputation as an anatomist is based."

Again (page 720), "Late in the seventeenth century Thomas Willis wrote on pertussis (1675) which by that time was thoroughly familiar. In his "Pathologiae cerebri et nervosi generis specimen" (Oxford, 1667) he also discussed infantile convulsions. He still dealt with the epilepsy convulsion complex as it had been defined by the ancients, and neither this account nor that of pertussis discloses marked clinical perspicacity. Both descriptions were extensively exploited as an opportunity to give an exposition of the peculiar physiological theories to which this author subscribed."

In calling him a dandy the prejudice toward Willis is obviously betrayed: it is perhaps based on the fact that he had a fashionable practice.

In the account given by Wood, who is often caustic in his descriptions and never withholds a critical comment, there is nothing to support this view, but rather the contrary. Wood wrote,

"Though Dr. Willis was a plain man of no carriage, little discourse, complaisance or society, yet for his deep insight, happy researches in natural and experimental philosophy, anatomy and chemistry, and for his wonderful success and repute in practice, the natural smoothness, pure elegance, delightful, unaffected neatness of Latin style none scarce have equaled, much less outdone him, how great so ever.

"When at any time he is mentioned by authors, as very often is done in words expressing their high esteem for his great worth and excellency, he is placed still as first in rank among physicians.

And further also he hath laid a lasting foundation of a body of physics chiefly in hypothesis of his own framing."

We shall later present testimony that tends to controvert some of the unfavorable opinions expressed by the detractors of Willis, and to prove that he was indeed a man of remarkable originality, profound learning, keen perception and prodigious industry and with all a man of extraordinary noble character.

Thomas Willis was born at Great Bedwyn in Wiltshire, Jan. 27, 1621.

He was sent to an excellent private school conducted by Mr. Sylvester, of Oxford. Wood in his "Athenae Oxienis" tells a little story of his early school days which in view of slurs by certain authors upon his character, as well as his ability, is worth quoting. "It might be added, as the boy is said to be father of the son, that Willis on his way to school would give his victuals away to the poor, who have a wonderful faculty for discovering generous people and never spare

them. His father, fearing that the boy would starve himself, compelled him to eat all his food at home." After a term in Mr. Sylvester's school, he enrolled as a student in the College of Christ Church. He received his B. A. degree in 1641; and his M. A. in 1642. About this time the King visited Oxford and in his train was the great Harvey. Was this the inspiration that prompted him to become a doctor of medicine?

Harvey did not allow the war or his duties as Royal physician to interfere with his medical investigations during his three years' residence at Oxford. We are told by Wood that he kept a hen in one of the University rooms in order to use the eggs at different stages of incubation for the study of embryology.

Willis may have been influenced also by other great medical investigators who were at Oxford at that time or had recently been there — namely, Francis Glisson (Glisson capsule), Thomas Wharton (Wharton's duct), Nathaniel Highmore (the antrum of Highmore).

Sydenham had begun his studies at Oxford, but being a Roundhead, he was now playing the part of a soldier in the Parliamentary forces bent upon the capture of the King's stronghold.

Willis joined the garrison in the royal defense, and it is said that during these days he spent all his available time in the pursuit of medical studies.

Parliamentary forces captured the city and took control of the University; but did Willis flee to London or to the country as did many of the King's partisans? Not at all, and in his staying we witness two things worthy of admiration: one, the conscientious resolution which guided Willis; the other, the tolerant spirit displayed by Cromwell.

Willis took a house opposite Merton College, where he gave refuge and sustenance to members of the clergy who were hated and persecuted by many of the followers of Cromwell ("a dangerous thing to do," remarks Wood), and here he set

up an oratory, where the Church of England service was daily conducted for the faithful who cared to resort there.

He was never molested, but was allowed to continue his studies, and actually received his degree, Bachelor of Medicine, under Parliamentary auspices. (The surrender to Fairfax took place on June 24, 1646. Willis was granted his degree Dec. 18 of that year.)

Willis remained in Oxford throughout the whole period of the Commonwealth, became very beloved as a physician and was sought far and wide by persons of all degree and all faiths.

He was noted for his piety and generosity; he gave his services without fee to the poor, and his Sunday earnings were given to charity.

Although very busy in the practice of medicine, Willis some way found time to devote to research and writing.

He was tremendously interested in all discussions concerning the cause and nature of disease and the means of cure, and he turned to the fundamental science for enlightenment.

As he says in the introduction of his treatise on the anatomy of the brain and nervous system, he was determined "not to pin my faith on the opinion of others nor yet on the opinion and guesses of my own mind, but for the future to believe only mature and accurate demonstration in order that a firm and stable basis may be laid."

He made careful studies especially in anatomy, physiology and chemistry; in anatomy by personal dissections, in physiology and chemistry by carefully conducted experiments. In his anatomical investigation he was fortunate in having the assistance of several young men of unusual talent animated like himself by the spirit of scientific inquiry.

Some authors have ascribed the chief merit of Willis' treatise on the anatomy of the brain and nervous system to two of these young men: Richard Lower, who later did some notable anatomical work on his own account, and Christopher

Wren, who became the famous Sir Christopher, architect of St. Paul and other celebrated structures.

Wren began as a medical student and being a good draftsman helped his chief by making anatomical drawings.

He is said to have devised the first instrument for making blood transfusions and he and Lower made the first recorded experiments in transfusing blood from one animal to another.

Willis in the introduction of his treatise gave full credit to these young men for their valuable assistance, and it is our guess that if the young men themselves, who were each 10 years younger than Willis, had said anything at all, they would have expressed their appreciation of the master genius in inspiring and directing their energies.

Admitting for argument's sake that in the case of his treatise on anatomy, chief credit belongs to his two talented assistants, those who belittle the genius of Willis must still explain the numerous other works of this author which exhibit equal originality and were acclaimed as masterpieces in the medical world of his day.

He wrote treatises on the following subjects: *1*. Fermentation. *2*. Fevers. *3*. The Urine. *4*. The Ascension of the Blood. *5*. Muscular Motion. *6*. Pathology of the Nervous System. *7*. Convulsive Diseases (Rational Therapeutics). *8*. The Scurvy. *9*. The Soul of Brutes.

All of these treatises were written in faultless Latin, and in his day were all immensely popular in medical circles at home and abroad.

Besides Wren and Lower, several other men at Oxford were deeply engaged in scientific studies and unmindful of the turmoil and strife going on all around them: Frances Bacon by the publication of his principles for the interpretation of nature had given great impetus to scientific investigation.

Progress could not be expected, as he showed by *a priori* argument and scholastic disputations with blind adherence to authority.

It was necessary to resort to accurate observation and experience and to apply the inductive method of reasoning to the information so attained.

Enthusiasm for research was aroused everywhere, but nowhere more than at Oxford.

In his "New Atlantis" he had suggested the formation of societies of learned men to concentrate on the discovery of the secrets of nature, and at Oxford a group of men including Thomas Willis was organized for this purpose under the name of the Philosophical Society. A similar group had begun meetings in London.

Shortly after the Restoration these two were amalgamated, and granted a charter by Charles II; and thus was born the famous Royal Society.

Bacon was particularly interested in the science of medicine. He wrote:

"Our physicians rely too much on mere haphazard, uncoordinated individual experience; let them experiment more widely, let them illuminate human with comparative anatomy, let them dissect and if necessary vivisect; and above all let them construct an easily accessible and intelligible record of experiments and results."

The Oxford men of medicine must have felt particularly close to Bacon; for instance, Harvey, who had been his personal physician. Quite remarkable is the fact that several of this group, who were closely associated with Willis in the studying of medical problems, rose in later life to the highest rank in other branches of science: we have already spoken of Sir Christopher Wren; before were John Locke, who later wrote "The Essay on Human Understanding," and came to rank as one of the world's great philosphers; and Sir William Pettys, who forsook medicine for the Science of Political Economy, often spoken of as the father of that science.

When Pettys was Professor of Anatomy at Oxford, and in that capacity had assigned to him for anatomical studies the bodies of condemned criminals, he gained great notoriety by

his resuscitation of a certain Anne Green, who was thought to be "hanged by the neck until she was dead." By his skill she was restored to life, and, so it was said, became a respectable citizen of the community.

Willis was distinguished no less as a philosopher than as a physician. In 1660, he received the appointment of Sedleian Professor of Philosophy at the University, replacing the incumbent, who was, as Wood bluntly puts it, "ejected" from that office.

After 30 years at Oxford, devoted to study, experimenting, writing, lecturing and the practice of medicine, Willis, on the special urging of the Archbishop of London, moved to the metropolis. His fame had preceded him, so that instantly he duplicated his success at the University City and became London's most distinguished physician, much sought after in fashionable and court circles.

It was natural to expect that he would now become Sir Thomas Willis and no doubt he could have done so except that he put conscience ahead of ambition.

When he was called in consultation in the case of the ailing son of the Duke of York, afterward James II, he diagnosed the case as "*mala stamina vitae.*" The King was shocked and took such offense that Willis from then on was *persona non grata* at court.

That he was absolutely right, however, in his diagnosis, there can be little doubt in the mind of any well informed physician, especially in view of subsequent family history:

James by his marriage with Anne Hyde had eight children, of which this sickly son was one. All the rest, except two daughters, Mary and Anne, died in early life. All the children, wrote a chronicler of the era, "were born with ulcers, or they broke out on them soon after; all were unhealthy and died young. His eldest daughter suffered with violent pains in the eyes, and Queen Anne, with gout due to dregs of the original taint."

William and Mary had no offspring. Poor Queen Anne had child after child, some say as many as 19, which did not live.

Willis took a house in historic St. Martins Lane not far from the church of St. Martins. As at Oxford, so in London, he was a faithful and devout churchman, and attended services twice daily. He rose early in the morning, in the winter at seven and summer at six, so that he could attend service before beginning his daily rounds.

Out of his funds he provided a special allowance which made it possible for services to be held at other than regular hours for those who, on account of their work, could not otherwise attend.

There should be no question but that Willis was a man of admirable character, kind, charitable, conscientious, steadfast, and one who would never sacrifice principle for preferment.

What should be said as to his ability? What place should be properly assigned him in medical history? If we accept the estimate of some of his detractors, he deserves no place at all; but there are some, of good authority, who think otherwise: Garrison ranks him among the great English clinicians, in the same class as Sydenham and Heberden, and praises him highly for his talent for close careful clinical observation — which led him to be the "first to establish the basic principle of diabetes melletus and other diseases." He gives him credit for being the first to describe epidemic typhoid fever, the first to describe and name puerperal fever. His work on nervous diseases, Garrison says, is justly esteeemed for its many striking clinical pictures, of which his descriptions of paralytic dementia is perhaps the most important. He refers to the fact that he was the first to describe the disease now designated as myastheria gravis.

Referring to his contribution to anatomy, his anatomy of the brain and nerves is said to be the most complete and accurate description that had been made up to his time, and it is notable that his classification of the cranial nerves continued to be standard for the next 200 years.

Giving him credit for the discovery of the accessory nerve, Garrison evidently does not agree with Mettler, who, as we noted, would deprive him of that honor. At any rate, it must be admitted that Willis added to the existing knowledge of the cranial nerve in his description of the pneumogastric or vagus nerve. Previous to his time, the various fibres attached to sympathetic were considered an integral part of the nerve.

W. S. Miller (Soc. Med. Hist., Chicago, 1923-1925, p. 227) has stressed his original work in the anatomy of lungs.

Malpighi by his microscopical studies had correctly indicated the structure of the lung.

By further experimental work Willis proved by direct injection of mercury into the blood vessels that there was not a general intercommunication between air spaces, as formerly believed, but that there were distinct areas marked off by connective tissues, each of which was supplied by a bronchial tube — a good description of what today are called secondary lobules of the lung.

If Dr. Willis had made no other advance in medical science than that of pointing out the significance of sugar in the urine, for that alone he deserves recognition as a great benefactor to the human race.

Before his time there had been some sort of association of excessive urination with wasting disease, but he was the first to indicate that this was particularly true of those cases where the was a sugary content.

He hit upon this idea by a simple expedient which no one before had thought of or had the courage to try; namely, tasting the urine.

It was the beginning of our understanding of the most important of all our metabolic disorders — one which is said to afflict no less than 2,000,000 people in the United States alone.

The priority of Willis in this field is recognized by Prof. Ralph H. Major in his excellent recent work entitled, "Classic Description of Disease."

His original description is reproduced under the title, "On the too much evacuation of the urine and its remedy; and especially of the disease or pissing evil, whose theory and method of curing is inquired into."

When comparing Willis with his great contemporary, Sydenham, one ought to bear in mind that while Sydenham was a clinician and little else besides, Willis, with his knowledge of practical medicine, was at the same time an anatomist, chemist, physiologist and philosopher; he was a profound student of the fundamentals of his art, and diligently engaged in scientific research and experimentation.

Sydenham cared little for theory and speculation but depended almost entirely upon his own individual experience. He employed the direct approach in his study of disease processes, and being an exceptionally keen observer and gifted with a natural instinct for recognizing resemblances and discarding nonessentials in the manifestations of disease, he gave to the profession the most lucid, concise and orderly description of disease processes it had ever possessed.

Willis was overfond of theory and speculation, and his tendency to indulge in them without restraint is the chief cause of his downfall, or rather we should say of his loss of favor in medical history.

His great fault was that in his description of disease, he aimed to paint a too perfect picture. He thought it was up to him, in every case, to give the whole answer.

In making these lengthy explanations, it was necessary to make them in terms of the prevailing theories of the day — so that we have much talk of humors, spirits, and fermentation, etc., which to modern readers is only a lot of meaningless jargon.

The effect is to weary the reader and to prejudice him against the author.

Sydenham, as we know, believed in humors, but he seldom mentions them. Avoiding such matter, fortunately for his reputation, he spoke a language which everyone can under- than "The Adventures of Gil Blas," an indirect way of saying the genito-urinary approach:

His disdain for preconceived opinions and authority is illustrated by the answer he once gave a medical student who asked him what book he should read in preparation for the study of medicine. His answer was that he knew none better than "The Adventures of Gil Blas," a rough way of saying that there is no other way to learn to treat disease than by close observation at the bedside.

Willis reveled in elaborate speculation, and he wrote so much that seems worthless that the average reader is inclined to believe that nothing he produced was worthwhile; however, if one has the patience to dig beneath the surface he will find some nuggets of pure gold. The amazing thing is that Willis darkly indicated much more than he openly produced. His work is actually rich in foreshadowings of future progress.

Michael Foster, one of his severest critics, admitted that he had dimly outlined the theory of reflex nerve action — a theory that was not brought to light until some hundred years later.

This is only one of his many prophetic visions. Careful search of his work revealed that he anticipated the modern doctrine of the vasomotor nerve action, internal secretion, metabolism, oxygenation of the blood in respiration and cerebral localization; and the workings of the subconscious mind.

Is not the vasomotion action remarkably well stated in the following?

"The small lines and cords of nerves, by acting on the muscular coat of the vessels to which they are distributed, do variously straighten, compress or it may be sometimes quite shut those blood carrying vessels."

Again, have we not an unmistakable forecast of the doctrine

of internal secretion in his description of the blood supply of the genitourinary approach:

"The blood pours forth something through the spermatic arteries, so that it receives as recompense a certain ferment from those parts — to-wit, certain particles imbued with a seminal tincture to the bloody mass which make it vigorous and inspire in it a new and lively virtue."

Still again, does he not give a certain intimation of the metabolic processes when in describing the fermentation, he speaks of it as a "process producing body charge by converting one element into another?"

It was not until 1775 that the great French chemist, Lavoisier, proved by his experiments the true nature of respiration; the oxygenation which took place when the air was inspired into the lungs, he showed was, in fact a combustion, identical with that which takes place outside of the body.

More than 100 years earlier Willis anticipated this discovery.

In his discussion of the physiology of the circulation, the heating of the blood likened to a fire or vital flame, and then he uses these explicit words: "and because blood first rushes into the lungs having there got an accession of air begins to burn."

Willis was the father of cerebral localization. As usual he went much further than his information justified and so made some egregious mistakes, when in a categorical manner he placed, for example, animal instincts in the corpora quadrigemera, certain vital functions in the cerebellum, etc.; but it was a beginning and a suggestion for future investigations which have proven of great importance in cranial surgery.

Finally, we may consider Willis as having laid the foundation of the doctrine of the subconscious mind, a doctrine developed by Freud and widely exploited in recent years both in medical and lay circles.

Willis in the latter years of his life devoted most of his

energies to philosophical subjects rather than to medicine pure and simple. In 1670, he wrote a treatise on hyseria, treating the subject from a psychological point of view, and in 1672 he brought out his treatise on the soul of brutes *(De aninma brutarum)*, an abtruse philosophical study which was much discussed at the time. He considered it his most important work and Osler has said that every physician desiring to be well-informed should read it.

While in lower animals there is but one soul, a corporeal one *(anima sensitiva)*, in men there are two, the corporeal and incorporeal.

The lower or bodily soul is divided into two parts, one in resident in the blood, and of the nature of flame, the other one in the nerves and of the nature of light.

The corporeal soul is the soul of appetite, passion, and of mechanical and rhythmical action. It can influence the rational soul and in turn be influenced by it.

This duality of the mind or its division into a reasoning and an automatic mind, he considered as illustrated by the case of the idiotic youth (mentioned in treatise on hysteria), who at each hour, exactly on the hour, had the habit of crying out clock-like throughout the 24 hours of the day, at exactly the right time.

While the work of Willis in psychology has received but scant attention from English or American writers, it has not been the same elsewhere.

In an article which appeared in the *Annales medico-psychologique* in 1928 (XVIII, p. 119), under the title *e*, "Un maitre de la psychiatrie au XVII^{ms} siecle, Thomas Willis" (17th century master of neuropsychiatry, Thomas Willis) the two authors, Jean Vichon and Jacques Vie, hail him as a great pioneer in this branch. By his powerful imagination, combined with acute reasoning, he anticipated in a remarkable way, they say, some of the modern thoughts and practices in this branch of medicine.

Willis is generally regarded as an "iatro-chemist," that is, one of those who believed that all the processes of nature were to be explained in chemical terms and that the care of diseases could accordingly be effected by chemical remedies.

He was so regarded because he followed Francois Sylvius, the head of that school, in adopting the idea of fermentation as an important agent in vital processes.

Willis, however, was not a strict adherent of this school; he adopted also some of the ideas advocated by the iatro-physcients, and he had some particular ideas of his own.

Willis has been criticized as a practitioner of polypharmacy.

Osler wrote: "When I look through the list of drugs that were given and the prescriptions that were then followed, I feel that the public has to thank the profession for having gotten rid of so many nauseous drugs.

"In some of Willis' prescriptions there were 10 to 15 ingredients, each worse than the other, besides vomits, purgings, sweatings, diuretics, cordials and opiates."

He was in this respect a follower of his times, but at that not so bad as the worst of them.

It was a frequent practice for physicians to administer prescriptions having 20 or 30 ingredients — and the pharmacopea of the period carried the famous "therica" which contained 64; besides it included as proper to be used preparation made of bile, urine, claws, teeth, hoofs, coxcombs, furs, feathers, isinglass, spiders' webs and many other offensive and impossible things — which I feel sure Willis never made use of. In fact, he sought to reform many of the irrational practices of his contemporaries in the use of remedies.

"They promise themselves," he wrote, "presently to cure all diseases and give them boldly in every case to the great injury and not infrequently to the destruction of the patient; so securely and rashly are these executioners accustomed to trifle with human life while they are led to the preparing and administering of these medicines in which always lurks some

venomous sting without any council or direction of method, but by mere chance and with a blend impetuosity."

That Willis was guided by scientific experiment rather than pure empiricism is evident by the fact that he investigated the effect of anatomical urine by injecting it into the veins of dogs. The vomiting that ensued he attributed to the explosion of animal spirits.

The effect of drugs in his opinion was chiefly due to their action upon spirits in the stomach.

His good judgment is evinced by the fact that he expressed his belief in the effectiveness of the comparatively new remedy, Peruvian bark (cinchona) in the cure of quartan fever.

In accordance with prevailing practice, he advocated depletives including venesection in cases of hemoptysis — but he deserves the highest praise for being the first to recommend a method of treating tuberculosis, the great importance of which was not recognized until these modern times.

The belief that the consumptive must be protected from the outside air rather than exposed to it continued strong in English medical as well as lay circles well into the nineteenth century.

Poor John Keats (1795-1821), a consumptive, was not only bled by his attending physicians after every hemorrhage but he was shut up in his room, with closed doors and windows and strictly admonished not to venture a step forth in the night air or during the least inclement weather.

Willis recognized that fresh air was of distinct value in his consumptive patients.

Referring to a particular case, he wrote, "The chiefest help accrued to him from the open air — for from thence he first began to recover his appetite, his digestion and sleep till at length he recovered his health."

Willis died from an attack of pneumonia, in all probability of influenzal origin — as an epidemic of apparent influenzal character was present at that time.

The high estimation in which he was held may be judged from the fact that he was accorded the honor of burial at Westminster, and this despite the fact that he was not loved by the King.

In 1731, his grandson, Brown Willis, who inherited his fortune, wishing to do him further honor, had erected a church in Buckinshire, where during his life a festival was held annually to commemorate the name of Thomas Willis.

It was called St. Martins, after the name of the church in which he worshipped in London.

Brown Willis was a distinguished antiquarian and an authority on old English cathedrals. During his life, he arranged to have a festival held yearly in the little town of Fenny Stratford, where he lived and where the church stood, and he provided in his will for the continuation of the ceremony after his death.

In November, 1916, Sir William Osler was the orator of the occasion.

A memorial of this nature was as appropriate as any that could be imagined to commemorate the life and works of a man who was such a devout churchman and distinguished no less for his goodness of heart than for his scholarly attainments.

THE AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

The annual meetings of the Triological Society and the Broncho-Esophagological Association will be held concurrently at the Drake in Chicago on April 18, 19 and 20, 1949. A joint meeting of these two societies will take place Tuesday morning, April 19. On the other days the Triological Society will meet in the mornings and the Bronchoscopic Society in the afternoons.

We also call your attention to these dates and places:

American Board of Otolaryngology—May 11-14, 1949, New York City.

American Laryngological Association — May 16-17, 1949, New York City.

American Otological Society—May 18-19, 1949, New York City.

In order to facilitate the coordination of national meetings, the Bronchoscopic, the Otological, the Laryngological and the Triological Societies are considering a five-year plan of dates and places. By adoption of such a scheme we hope to reduce the traveling mileage and the amount of time away from our offices. For additional information, write to Dr. C. Stewart Nash, Secretary, 708 Medical Arts Building, Rochester 7, N. Y.

MISSISSIPPI VALLEY MEDICAL SOCIETY MEETS AT ST. LOUIS, SEPT. 28, 29, 30, 1949.

The Fourteenth Annual Meeting of the Mississippi Valley Medical Society will be held at the Jefferson Hotel, St. Louis, Mo., Sept. 28, 29, 30, 1949, under the presidency of Dr. Alphonse McMahon, of St. Louis University. At the recent current meetings of the Society and board of directors, the following officers were elected: Dr. Nathaniel G. Alcock, Iowa City, Iowa, President-elect; Dr. Wendell G. Scott, St. Louis, Mo., First Vice-President; Dr. Charles F. Harmon, Springfield, Ill.; Second Vice-President; Dr. John I. Marker, Davenport, Iowa, Third Vice-President; Dr. Harold Swanberg, Quincy, Ill., Secretary-Treasurer; Dr. Ralph McReynolds, Quincy, Ill., Accounting Officer.

INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY, LONDON, 1949.

The British Association of Otolaryngologists is organizing the Fourth International Congress of Otolaryngology, to be held in London from July 17 to July 23, 1949. There will be further meetings, for those who wish to go, at Oxford, Cambridge and Edinburgh on July 25 and 26. It is hoped that a full academic program will be arranged, and also various social functions.

The secretaries of the National Otolaryngological Societies have been circularized and asked to send a list of their members for individual notification. Should any association not receive this letter, they should communicate with the General Secretary, F. C. W. Capps, F.R.C.S., 45, Lincoln's Inn Fields, London, W.C. 2.

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AN OTOLARYNGOLOGY.

The next meeting of the Central Illinois Society of Ophthalmology and Otolaryngology will be held at the Pere Marquette Hotel, Peoria, Ill., on April 22, 23 and 24.

Dr. D. J. Lyle, professor of ophthalmology at the Medical College and director of the service of the University of Cincinnati, will lecture on *1.* Clinical Diagnosis from Lesions of the Visual System; *2.* Eye Involvement Resulting from Head Injuries; *3.* Clinical Study of Vascular Affections of Brain and Eye. Dr. B. E. Ellis, associate professor of otolaryngology, Indiana University, will lecture on *1.* Congenital Cysts of the Head and Nasal Bridge; *2.* Congenital Cysts of the Neck; *3.* Rhinoplasty Procedures in the Practice of Otolaryngology. Dr. Walter Stevenson, Jr., Quincy, Ill., and other active members will discuss some pertinent eye, ear, nose and throat subjects.

HEARING AIDS ACCEPTED BY THE COUNCIL ON PHYSICAL MEDICINE OF THE AMERICAN MEDICAL ASSOCIATION.

As of February 1, 1949.

Acousticon Model A-100.
Manufacturer: Dictograph Products Corp., 580 Fifth Ave., New York 19, N. Y.

Aurex (Semi-Portable); Aurex Model C-B, Model C-A, Model F and Model H.
Manufacturer: Aurex Corp., 1117 N. Franklin St., Chicago, Ill.

Beltone Mono-Pac; Beltone Harmony Mono-Pac.
Manufacturer: Beltone Hearing Aid Co., 1450 W. 19th St., Chicago, Ill.

Dysonic Model 1.
Manufacturer: Dynamic Hearing Aids, 43 Exchange Pl., New York 5, N. Y.

Electroear Model C.
Manufacturer: American Earphone Co., Inc., 10 East 43rd St., New York 17, N. Y.

Gem Hearing Aid Model V-35.
Manufacturer: Gem Ear Phone Co., Inc., 50 W. 29th St., New York 1, N. Y.

Maico Type K; Maico Atomeer.
Manufacturer: Maico Co., Inc., North Third St., Minneapolis, Minn.

1947—Mears Aurophone Model 98; Mears Aurophone Model 200.
Manufacturer: Mears Radio Hearing Device Corp., 1 W. 34th St., New York, N. Y.

Micronic Model 101 (Magnetic Receiver).
Manufacturer: Micronic Co., 727 Atlantic Ave., Boston 11, Mass.

Microtone T-3 Audiomatic; Microtone T-4 Audiomatic; Microtone T-5 Audiomatic.

Manufacturer: Microtone Co., 4602 Nicollet Ave., Minneapolis 9, Minn.

National Cub Model; National Standard Model; National Star Model.

Manufacturer: National Hearing Aid Laboratories, 815 S. Hill St., Los Angeles 14, Calif.

Otarion Model A-1; Otarion Model A-3; Otarion Models A-4 J and S; Otarion Model E-1; Otarion Model E-1S; Otarion Model E-2.

Manufacturer: Otarion Hearing Aids, 159 N. Dearborn St., Chicago, Ill.

Paravox Models VH and VL; Paravox Model XT; Paravox Model XTS.

Manufacturer: Paraphone Hearing Aid, Inc., 2056 E. 4th St., Cleveland, Ohio.

Precision Table Hearing Aid.

Manufacturer: Precision Electronics Co., 850 W. Oakdale, Chicago 14, Ill.

Radioear 45-CM; Radioear Model 45-M-magnetic air conduction receiver; Radioear Model 45-M-magnetic bone conduction receiver; Radioear Permo-Magnetic Uniphone.

Manufacturer: E. A. Myers & Sons, 306 Beverly Rd., Mt. Lebanon, Pittsburgh, Pa.

Ravox (Semi-Portable).

Manufacturer: Zenith Radio Corp., 6001 W. Dickens Ave., Chicago, Ill.

Silver Micronic Hearing Aid Model 101; Silver Micronic Hearing Aid Models 202M and 202C.

Manufacturer: Micronic Corp., 101 Tremont St., Boston 8, Mass.

Solopak Hearing Aids.

Manufacturer: Allen-Howe Electronics Corp., 150 Main St., Peabody, Mass.

Sonotone Audicles No. 530, No. 531 and No. 533; Sonotone Model 600; Sonotone Model 700; Sonotone Model 900.

Manufacturer: Sonotone Corp., Elmsford, N. Y.

Superfonic Hearing Aid.

Manufacturer: American Sound Products, Inc., 2454 S. Michigan Ave., Chicago, Ill.

Telex Model 22; Telex Model 97; Telex Model 612; Telex Model 900; Telex Model 1020; Telex Model 1550.

Manufacturer: Telex, Inc., Minneapolis 1, Minn.

Tonemaster Model Royal.

Manufacturer: Tonemasters, Inc., 1627 Pacific Ave., Dallas 1, Tex.

Trimm Vacuum Tube No. 300.

Manufacturer: Trimm, Inc., 400 W. Lake St., Libertyville, Ill.

Unex Model "A."

Manufacturer: Nichols & Clark, Hathorne, Mass.

Vactuphone Model 3.

Manufacturer: Allen-Howe Electronics Corp., Salem, Mass.

Western Electric Orthotronic Model; Western Electric Model 63; Western Electric Model 64; Western Electric Models 65 and 66.

Manufacturer: Western Electric Co., Inc., 120 Broadway, New York 5, N. Y.

Zenith Radionic Model A-2-A; Zenith Radionic Model A-3-A; Zenith Radionic Model B-3-A; Zenith Model 75.

Manufacturer: Zenith Radio Corp., 6001 Dickens Ave., Chicago, Ill.

All of the accepted hearing devices employ vacuum tubes.

DIRECTORY OF OTOLARYNGOLOGIC SOCIETIES.

AMERICAN OTOLOGICAL SOCIETY.

President: Dr. Marvin F. Jones, 121 E. 60th St., New York 22, N. Y.
Secretary: Dr. Gordon D. Hoople, Medical Arts Bldg., Syracuse 3, N. Y.
Meeting: New York, N. Y., May 18-19, 1949.

AMERICAN LARYNGOLOGICAL ASSOCIATION.

President: Dr. Frederick T. Hill, Professional Bldg., Waterville, Me.
Secretary: Louis H. Clerf, 1530 Locust St., Philadelphia 2, Pa.
Meeting: New York, N. Y., May 16-17, 1949.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. John J. Shea, 1018 Madison Ave., Memphis, Tenn.
Secretary: Dr. C. Stewart Nash, 708 Medical Arts Building, Rochester, N. Y.
Annual Meeting: Chicago, Ill., Hotel Drake, April 18-20, 1949.

AMERICAN MEDICAL ASSOCIATION, SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY.

Chairman: Dr. Fletcher D. Woodward, 104 E. Market St., Charlottesville, Va.
Secretary: Dr. James M. Robb, 641 David Whitney Bldg., Detroit, Mich.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Conrad Behrens, 35 E. 70th St., New York, N. Y.
President-Elect: Dr. J. Mackenzie Brown, 1136 W. 6th St., Los Angeles, Calif.
Executive Secretary: Dr. William L. Benedict, Mayo Clinic, Rochester, Minn.

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY.

President: Dr. Rea E. Ashley, 384 Post St., San Francisco, Calif.
Secretary-Treasurer: Dr. Joseph Hampsey, 806 May Bldg., Pittsburgh 22, Pa.

AMERICAN BOARD OF OTOLARYNGOLOGY.

Meeting: New York, N. Y., May 11-14, 1949.

PAN AMERICAN ASSOCIATION OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY.

President: Prof. Justo Alonso.

Secretary: Dr. Chevalier L. Jackson, 255 S. 17th St., Philadelphia, Pa.

Second Pan American Congress of Oto-Rhino-Laryngology and Broncho-Esophagology: Montevideo, January, 1950

AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION.

President: Dr. Paul Holinger, 700 N. Michigan Ave., Chicago 11, Ill.

Secretary: Dr. Edwin N. Broyles, 1100 N. Charles St., Baltimore 1, Md.

Meeting: Chicago, Ill., April 18-20, 1949.

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Colby Hall.

Secretary-Treasurer: Dr. Warren A. Wilson.

Chairman of Section on Ophthalmology: Dr. John A. Bullis.

Secretary of Section on Ophthalmology: Dr. Rodman Irvine.

Chairman of Section on Otolaryngology: Dr. Leland G. Hunnicutt.

Secretary of Section on Otolaryngology: Dr. Alden H. Miller.

Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd., Los Angeles, Calif.

Time: 6 P.M., fourth Monday of each month from September to May, inclusive.

AMERICAN OTORHINOLOGIC SOCIETY FOR THE ADVANCEMENT OF PLASTIC AND RECONSTRUCTIVE SURGERY.

President: Dr. Alfred Schattner, 115 E. 61st Street, New York 21, N. Y.

Secretary: Dr. Norman N. Smith, 291 Whitney Avenue, New Haven 11, Conn.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Chairman: Dr. Kate Savage Zerfoss, 165 Eighth Ave., North Nashville 3, Tenn.

Chairman-Elect: Dr. Calhoun McDougall, 703 Medical Arts Bldg., Atlanta 3, Ga.

Vice-Chairman: Dr. V. R. Hurst, 315 N. Center St., Longview, Tex.

Secretary: Dr. Alston Callahan, 908 S. Twentieth St., Birmingham 5, Ala.

THE PHILADELPHIA LARYNGOLOGICAL SOCIETY.

President: Dr. M. Valentine Miller, 114 W. Phil-Ellen St., Philadelphia, Pa.

Vice-President: Dr. Thomas F. Furlong, Jr., 36 Parking Plaza, Ardmore, Pa.

Treasurer: Dr. Harry P. Schenck, 1912 Spruce St., Philadelphia, Pa.

Secretary: Dr. William J. Hitschler, 5 E. Chestnut Hill Ave., Philadelphia 18, Pa.

SOCIEDAD NACIONAL DE CIRUGIA OF CUBA.

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Secretario: Dr. René Smith.

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Tesorero: Dr. Antonio Rodrigues Diaz.

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ASSOCIACAO MEDICA DO INSTITUTO PENIDO BURNIER — CAMPINAS.

President: Dr. Joao Penido Burnier.

First Secretary: Dr. Gabriel Porto.

Second Secretary: Dr. Roberto Barbosa.

Librarian-Treasurer: Dr. Leoncio de Souza Queiroz.

Editors for the Archives of the Society: Dr. Guedes de Melo Filho, Dr. F. J. Monteiro Sales and Dr. Jose Martins Rocha.

SOCIEDAD DE OTORRINOLARINGOLOGIA Y BRONCOESOFAGOSCOPIA DE CORDOBA.

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Vice-Presidente: Dr. Luis E. Olsen.

Secretario: Dr. Eugenio Romero Diaz.

Tesorero: Dr. Juan Manuel Pradales.

Vocales: Dr. Osvaldo Suárez, Dr. Nondier Asis R., Dr. Jorge Bergallo Yofre.